HISTOPATHOLOGICAL STUDY OF SOFT TISSUE TUMOURS AND CORRELATION OF HISTOLOGIC GRADE OF SOFT TISSUE SARCOMAS WITH PROLIFERATIVE MARKER KI 67 IN SELECTED CASES

DISSERTATION SUBMITTED FOR

M.D.PATHOLOGY

(BRANCH-III)

THE TAMILNADU DR.M.G.R.MEDICAL UNIVERSITY

CHENNAI, TAMILNADU

APRIL – 2017

CERTIFICATE FROM THE DEAN

This is to certify that the dissertation entitled "HISTOPATHOLOGICAL STUDY OF SOFT TISSUE TUMOURS AND CORRELATION OF HISTOLOGIC GRADE OF SOFT TISSUE SARCOMAS WITH PROLIFERATIVE MARKER KI 67 IN SELECTED CASES" submitted by Dr.S.Raasi to the Faculty of Pathology, The Tamilnadu Dr.M.G.R. Medical University, Chennai in partial fulfilment of the requirement for the reward of M.D. Degree in Pathology is a bonafide work carried out by her during the period 2014-2016.

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I, **Dr.S.RAASI,** solemnly declare that the dissertation titled "**HISTOPATHOLOGICAL STUDY OF SOFT TISSUE TUMOURS AND CORRELATION OF HISTOLOGIC GRADE OF SOFT TISSUE SARCOMAS WITH PROLIFERATIVE MARKER KI 67 IN SELECTED CASES"** is a bonafide work done by me at Department of Pathology, Madurai Medical College & Government Rajaji Hospital, Madurai during the period from July 2014 to August 2016.

I also declare that this bonafide work or a part of this work was not submitted by me or any other for any reward, degree and diploma to any university, board either in India or abroad.

This dissertation is submitted to The Tamilnadu Dr.M.G.R. Medical University, towards partial fulfilment of requirement for the reward of **M.D. Degree in PATHOLOGY.**

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ACKNOWLEDGEMENT

My profound thanks and gratitude to **The Dean,** Madurai Medical College and Government Rajaji Hospital, Madurai and the Ethical committee for permitting me to carry out this study.

I wish to express my heartfelt thanks to the respected Professor **Dr.T.Geetha, M.D.,** Professor and head of the Department of Pathology, Madurai Medical College, Madurai for her valuable suggestions, constant encouragement and guidance throughout this work.

I express my gratitude to all the Professors **Dr.G.Meenakumari,M.D., Dr.N.Sharmila Thilagavathy, M.D., Dr.M.Sivakami, M.D.,** and all the Assistant Professors and Tutors for their valuable suggestions and guidance in this work.

I am grateful to Professor and Head of the department of Surgery and Professor and Head of the department of Surgical Oncology, Government Rajaji Hospital, Madurai for permitting me to carry out this study.

I am indebted to my fellow post graduates and technical staff of the Department of Pathology for their immense help in carrying out this study.

CONTENTS

INTRODUCTION

INTRODUCTION

Soft tissue tumours are highly heterogenous group of tumours that are classified histologically according to their resemblance to adult mesenchymal tissue.[1] Benign tumours outnumber malignant soft tissue tumours. Malignant soft tissue tumours constitute only less than 1 % of all malignant neoplasms.[2] Gender and age related incidence vary among histologic types.[1] Most common sites for soft tissue sarcomas include deep soft tissues of extremities, chest wall, mediastinum and retroperitoneum.

Benign lesions have low rate of local recurrence[1] and require conservative therapy. In malignant lesions, there is high rate of local recurrence and distant metastasis and require adjuvant treatment modalities. Immunohistochemistry for tissue-related markers is of great value and is extensively used to accurately classify these neoplasms.[1] Thus the histopathological classification of soft tissue tumours based on their behavior is important to decide the treatment.

FNCLCC grading is the standard grading system used in the morphological evaluation of sarcomas based on tumour differentiation score, mitoses and volume of tumour necrosis[3]. Low grade lesions are usually well differentiated. Intermediate grade lesions are either locally aggressive or rarely metastasizing[1]. Poorly differentiated lesions are high grade lesions[1]. Hence histologic grading of

sarcomas is essential in predicting the prognosis of sarcomas based on morphology.

Since histologic grading is prone for subjective variation, many prognostic markers have been evaluated in soft tissue sarcomas. Most promising proliferative marker to assess the risk of distant metastasis and tumour mortality in sarcomas is Ki-67.[4,5,7,10] Prospective evaluation of Ki-67 can be used for predicting the overall survival rate in patients with sarcomas and accordingly the treatment can be planned.

AIMS AND OBJECTIVES

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- To study the frequency of occurrence of soft tissue tumours in specimens received at the Department of pathology, Madurai medical college, Madurai.
- To study age, sex and site related incidence of soft tissue tumors.
- To study the histopathological features of benign and malignant soft tissue tumors.
- To classify soft tissue tumours according to World Health Organisation classification.
- To assess the histologic grade of soft tissue sarcomas morphologically by FNCLCC (Federation Nationale des Centres de Lutte Contre le Cancer) grading system.
- To correlate the histologic grade with expression of Immunohistochemical proliferative marker Ki 67 in selected cases of soft tissue sarcomas.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Soft tissue is defined as non-epithelial and extraskeletal tissue of the body.[1] It is composed of adipose tissue, fibrous tissue, smooth muscle, blood vessels, lymphatics, skeletal muscle and peripheral nervous system.[1] Soft tissue tumors are uncommon and comprise about 2% or less of surgical pathology cases.

HISTORICAL ASPECTS:

- "Soft tissue" was first introduced by Wardrab in the year 1782.
- The term sarcoma originated from the Greek language and means "fleshy growth".
- Rokitansky was the first to give classification of soft tissue tumours in 1842.[12]
- Lebert was the first to observe the microscopic features of sarcomas in 1845.
- Weber described "Rhabdomyosarcoma" in 1854 but Arthur Purdy Stout was the first to separate it as a distinct entity.[13]
- Virchow in 1858 identified that the connective tissue was the origin of soft tissue tumours.[12]

- Arthur Purdy in 1918 found a tumor composed of undifferentiated small round cells which formed rosettes.[14]
- Adair et al in 1932 on his extensive study on adipocytic tumours found that lipomas were the most common soft tissue tumours.[15]
- Stobbe described embryonal type of rhabdomyosarcoma as a separate entity in 1950.[16]
- Maccollum et al in 1956 on his study on haemangiomas reported that capillary haemangioma is the commonly seen in infants and children.[17]
- Horn RC et al gave the classification of Rhabdomyosarcoma and Enterline et al described its alveolar type as a distinct one in the year 1958.[18]
- Enzinger FM was the first to describe clear cell sarcoma of the soft tissue in 1968.[19]
- Enzinger FM defined "Soft tissues" as non-epithelial and extraskeletal tissues of the body excluding the glia, reticuloendothelial system and supporting tissues of various internal organs.[1]
- Enzinger in 1970 described the morphology of 'Epithelioid sarcoma'.[20,21]
- Extraskeletal chondrosarcoma was first described by Enzinger and Shiraki in 1972.[22]

- In 1975, Enzinger and Angervall described the first case of extraskeletal Ewing's sarcoma.[23]
- Russell et al in 1977 proposed the clinical staging system of soft tissue tumours in their study.[24,25]
- Hasegawa T et al observed that the tumour grade obtained using the MIB-I score was a strong prognostic factor in his study on patients with soft tissue sarcomas in 2003.[26,27]
- WHO in 2013 divided soft tissue tumors broadly into adipocytic, fibroblastic/myofibroblastic, fibrohistiocytic, skeletal muscle, smooth muscle, vascular, perivascular, peripheral nerve sheath tumours, undifferentiated/ unclassified tumours and lastly of uncertain differentiation.[28]

EMBRYOLOGY:

Embryologically, soft tissues are mainly derived from mesoderm and partly from neuroectoderm corresponding to the peripheral nerves.[1]

HISTOLOGY:

Fibrous tissue consists primarily of fibroblasts and an extracellular matrix that contains fibrillary collagen and elastin and nonfibrillary extracellular matrix. Fibroblasts are responsible for the production of the various extracellular materials, including collagen. Their shape varies from spindle (especially when stretched

along bundles of collagen fibers) to stellate (in myxoid areas). Myofibroblasts are modified form of fibroblasts with features intermediate between fibroblasts and smooth muscle cells.[29]

Adipose tissue is divided into two major types: white fat, commonly situated in the subcutaneous tissue, retroperitoneum and abdomen and brown fat, commonly located in the interscapular region, neck, axilla and retroperitoneal areas around kidneys. Brown fat is abundant in infants and children. White fat adipocytes are round or oval cells having vacuolated cytoplasm due to a single large lipid droplet that pushes the crescent-shaped nucleus to the periphery. Brown fat cells are smaller round or polygonal cells with eosinophilic cytoplasm composed of multiple vacuoles and a centrally located nucleus showing fine indentations.[29]

Skeletal muscle is mainly derived from within myotomes (but also from mesoectoderm in the head and neck region) through the formation of myoblasts and eventually of myotubes (muscle fibers).The most distinguishing feature of these fibers is the presence of myofibrils with two types of microfilament: thin actin and thick myosin. The periodic arrangement and interdigitation of thin and thick filaments results in the cross-banding seen at a light microscopic level. The I (isotropic) band is made only of thin filaments, the adjacent A (anisotropic) band is a zone of overlapping thin and thick filaments, and the H band is made up only of

thick myofilaments. The I band is divided in its center by the Z line or disc, which is thought to serve as an attachment site for the sarcomere.[29]

Vessels are divided into blood vessels and lymph vessels. Blood vessels are further subdivided into arteries, veins and capillaries. Endothelial cells lining the blood vessels form the major group and perivascular cells include pericytes, glomus cells and smooth cells[1,30]. Lymph vessels have endothelial lining.

Peripheral nerves are composed of axons, Schwann cells, perineurial cells, and fibroblasts.[31] Fibroblasts are located in the epineurium. Each nerve fascicle is surrounded by the perineurium, a structure continuous with the pia arachnoid of the central nervous system. Schwann cells are of neuroectodermal derivation, whereas perineurial cells apparently originate from fibroblasts.[32-34]

ETIOLOGY AND RISK FACTORS FOR SOFT TISSUE TUMOURS:

Pathogenesis of most soft tissue tumours is not known.[1] Recognised causes are exposure to ionizing radiations, inherited or acquired immunologic defects, trauma, fractured site with implants[35] usually after a latent period of several years. Other risk factors include herbicides like phenoxyacetic acids and chlorophenol containing wood preservatives.[36]

RADIATION THERAPY:

External radiation therapy is a well-documented risk factor for soft tissue sarcomas.[37-39] The incidence of reported sarcomas following therapeutic irradiation is low, ranging from 0.03% to 0.3%.[1] The latency period is between 5 and 10 years, with the most common post radiation sarcoma being undifferentiated pleomorphic sarcoma.[1] The median reported total irradiation dose varies but is generally above 40 Gy, with sarcomas reported to develop after only 12 Gy. In a large review of 565 patients with sarcoma as a second malignancy, 160 (28%) were considered to have a radiation-associated sarcoma.

VIRUSES AND IMMUNOLOGIC FACTORS:

Two DNA viruses of the herpes virus family have been linked to specific types of soft tissue sarcomas: human herpesvirus 8 (HHV8) to Kaposi's sarcoma[40,41] and Epstein-Barr virus (EBV) to certain leiomyosarcomas and are more common in immunosuppressed patients.[42] Angiosarcomas can occur due to chronic lymphedema[43] following radical mastectomy and is known as Stewart- Treves syndrome. This is due to the loss of regional immune surveillance.[44]

HEREDITARY SARCOMA:

A number of syndromes are associated with STS development. These are most often due to mutations in tumor suppressor- , growth factor- and growth factor receptor genes and translocations forming new potent fusion-genes and proteins.[1] The list of most common cancer syndromes leading to STS include Li Fraumeni, neurofibromatosis type I (Von Recklinghausen's) and type II,[47,48] familial adenomatous polyposis (FAP)/Gardner,[49] Retinoblastoma,[50,51] Werner,[1] Lynch syndromes[1] and tuberous sclerosis/Burneville disease.[1]

INCIDENCE AND DISTRIBUTION OF SOFT TISSUE TUMOURS IN RELATION TO AGE, SEX, SITE:

Enzinger F.M. & S.W. Weiss 1983, Robbins et al 1994, Myhre Jenson et al 1981[52] reported an incidence of soft tissue tumors as 0.8-1%, 0.8% and < 2% respectively. Stout AP [54] & Lattes R[55], Angervall et al 1987, Enzinger, F. M. S. W. Weiss 1988 reported a benign to malignant ratio as 5:1 and 18.5 to 100:1 respectively.

Dev et al**,** Cotran et al 1994 reported an incidence of 58% in males, Costa j et al[56] 1984 observed an incidence of 55-60% in males. Myhre Jenson O et al[53] 1983, Trojani et al 1984[3], Tsuji Moto M et al 1988[57,58], noted an incidence of 55-60% in males. The general site distribution of soft tissue tumors as reported by Robbin et al 1994 was 10% in head and neck region, 30% in trunk, 20% in upper extremities,

40% in lower extremities. According to Costa J et al[56] 1984, W.L. Natrajan et al[59] 1987, the site distribution of benign soft tissue tumours were 4-9% in head & neck, 32% in trunk and 60-64% in extremities.

BENIGN SOFT TISSUE TUMOURS:

- Lipomas were common in 5th and 6th decade with a mean of 42-50 years as per FE Adair[15] 1932, TK Das Gupta[60] 1969, Rydholm A Berg No[61] 1983. The peak incidence was also seen in the first decade and head and neck was the common site involved.
- The age incidence of neurilemoma was between 20-30 years in study by Enzinger FM 1988 and site predilection was flexor aspects of extremities. Sex incidence of peripheral nerve tumors was observed to be equal in studies done by Evans[62] 1980, Enzinger FM 1988, Oberman & Sullenger[63] 1967. In the series by Geschickter[64] 1935 about 90% neurofibromas were of solitary type.
- In the study carried out by Mark J Kransdorf[65], mean age for benign fibrous histiocytoma was 33 years. In the study carried out by Calonje E et al[66], there was predominance in males for BFH (male/female ratio 1.9:1) and common sites were upper extremities (34%), lower extremities (27%), and head and neck region (20%).

- In the study carried out by Mark J Kransdorf[65], mean age for lymphangioma was 19 years, most common site was retroperitoneum followed by lower extremity and head and neck and there was male predominance.

MALIGNANT SOFT TISSUE TUMOURS:

- The incidence of liposarcoma reported by Costa J et al[56] 1988 was 10-25% among soft tissue tumors. AFIP, Reszel et al[67] 1966 and Spittle et al[68] 1974. Stout AP[53] Lattes R[54] and Kindblomtt[69] et al 1978 reported a male preponderance.
- Fibrosarcomas constituted about 5-10% of sarcomas according to Markhede G et al[70] 1981. Enzinger FM & Weiss SW 1988 reported fibrosarcomas in the average age as 45 years. Iwasaki H & Enjoji M[71] 1979 reported an age incidence ranging from 40-70 years with an average at 47.7 years. In a review of 695 cases at AFIP 1970-79, site distribution was 10% in head and neck, 17% trunk, 28% in upper extremities & 45% in lower extremities. Hidayat AA[72] 1983 and Enzinger FM & SW Weiss 1988 reported site distribution of 85-90% in extremities in which 50-60% was in lower extremity, 10-15% occurred in head and neck and trunk region.
- Gutierez G et al[73] 1984 reported an incidence of 1.1% of Dermatofibrosarcoma protuberans of all the soft tissue sarcomas and 0.06%

of all malignant tumors. He reported an age incidence between the ages of 30-50 years and a male predominance accounting to 36%. Males were more frequently affected as reported by Enzinger FM & Weiss SW 1988. In a review of 853 cases at AFIP 1960-79 the site distribution was noted to be 14.5% in head and neck, 47.4% in trunk, 18.2% in upper extremities and 19.9% in lower extremities.

- In the study done by Anders Rydholm[74] 1986, out of 278 soft tissue sarcomas, 22% were malignant fibrous histiocytoma. Hashimoto H et al[75] 1984, Costa j et al[56] 1984 & Lawrence et al 1987 stated that 12-33% of soft tissue sarcomas were MFH[76]. As per Enzinger et al 1978, in an analysis of 200 cases of MFH an age range was obtained between 50-70yrs. Kyriakos M 1972 & Hashimoto H 1984 have the same age incidence[76]. Rooser B et al[77] 1991 reported a sex incidence of M: F 1.1:1. Obrein and Stout[78] 1964, De Rosai & Lattes reported major site as in lower extremity followed by chest wall, upper extremity and retroperitoneum.
- Dimitris P, Agamandis in 1986 reported an incidence of Rhabdomyosarcoma as 19% of all soft tissue malignancies[76]. AFIP study of 558 cases during 1970-79 reported more than 50% incidence of embryonal type of Rhabdomyosarcoma below 10 years of age and a 2nd peak at 15-20

years (Alveolar type)[1]. Bale PM 1983 reported an incidence of 66% below 10 years of age[79].

- Russel WO et al[24] 1977, Hashimoto H et al[80] 1985 quoted an incidence of about 7% of leiomyosarcomas out of all soft tissue tumors. A study by Alan G et al[81] 1981 revealed 28 cases of leiomyosarcomas. Out of 28 cases, 16 cases occurred in the retroperitoneum, 3 arising in blood vessels and 9 from peripheral deep soft tissues, forming incidence 57%, 11% and 32% respectively. AFIP, Enzinger FM, Weiss SW 1988, Anderson 1990, reported female predominance[76]. A study of 80 cases of leiomyosarcomas by Helwig & Field[82] 1977 revealed the site distribution of 45% in lower extremities. In a review of 250 leiomyosarcomas of soft tissue filed in surgical pathology of Columbia University 1977 revealed 116 cases arising from lower extremity including gluteal region (46.4%)[76].
- Synovial sarcoma constituted about 6-15% of all sarcomas as per Costa. J. et al 1988[56]. In a review of 418 cases, Geiler found the average age to be at 35 years and 2.6% incidence under 10 years of age[76]. Zito in review of 48 cases[83] and Leslie A et al[84] 1986 found that synovial sarcoma occurred in young adults. Studies by Mackenzie DH[85] 1977, revealed M: F ratio to be 1.4:1 to 2:1, Cagle LA[86] et al 1987 reported roughly equal incidence in both sexes. Review by Leslie A et al[84] 1986 of 63 cases, found lower extremities

to be the common site. In a review of 141 cases on the records of surgical pathology division of Columbia university revealed 61 cases (43.3%) in lower extremities including 9 cases in foot, 44 cases (31.2%) in trunk and 13 cases (9.2%) in head & neck region[76].

- Extraskeletal Ewing's sarcoma is usually found in young adults and has slight predominance in male patients. Few cases affecting patients beyond 50 years were reported by Carol C.Cheung, Rita.A, Kandel, Raymound, E.Mathews and Robert S.Bell[76]. Extraskeletal ewings sarcoma frequently involves soft tissue of chest wall, paravertebral region, extremities and retroperitoneum as given by Enzinger. In series by Pitchard et al 1975, patients ranged in age from 14 months to 59 years and 70% were younger than 10 years[87].
- Extraskeletal chondrosarcoma is more common in men of age group 44 to 49 years. It involved extremities as given by Brooks JSJ in Disorders of soft tissue tumours and Sternberg. An intra-abdominal case was reported by Farah Gaudier in 2003[88].
- Epithelioid sarcoma, primarily seen in hand and wrist was described by Evans HL, Baer SC[89]. Females usually outnumbered males as studied by Mirra JM, in 1972[90].

MORPHOLOGY OF BENIGN AND INTERMEDIATE MALIGNANT POTENTIAL SOFT TISSUE TUMOURS:

ADIPOCYTIC TUMOURS:

LIPOMA:

Morphologically, lobules of mature adipocytes with univacuolated cytoplasm and eccentrically placed crescentic nuclei are seen in lipomas. There are many variants of lipoma such as angiolipoma, myolipoma, myelolipoma, chondroid lipoma, intramuscular, intermuscular lipomas, neural fibrolipoma and spindle cell/ pleomporphic lipoma. In Spindle cell lipoma, spindle cells are arranged haphazardly and in short parallel bundles with elongated nucleus and bipolar cytoplasmic processes. Myxoid matrix, ropy collagen, mast cells are conspicuous features seen in spindle cell lipoma[91]. Pleomorphic lipoma characteristically contains floret giant cells, ropy collagen, myxoid matrix and mast cells[92].

Due to their common incidence, lipomas are excluded from our study.

WELL DIFFERENTIATED LIPOSARCOMA / ATYPICAL LIPOMATOUS NEOPLASM:

This is an intermediate locally aggressive soft tissue tumour composed of mature adipocytes with slight variation in size and atypical hyperchromatic nuclei.

Multivacuolated lipoblasts with indented nuclei are seen. Its variants include lipoma like type, inflammatory type with prominent lymphoplasmacytic infiltration and sclerosing type with dense fibrillary collagenous stroma with atypical cells[93].

FIBROBLASTIC/ MYOFIBROBLASTIC TUMOURS:

FIBROMATOSIS:

The tumour cells are bland stellate to spindle shaped and seen in a dense collagenous stroma. Some areas may contain keloid type collagen. Many thin walled veins and thick walled arteries may be seen. Inflammatory infiltrate are seen in the advancing edge of the tumor[94].

DERMATOFIBROSARCOMA PROTUBERANS OF INTERMEDIATE MALIGNANT POTENTIAL:

This is an apparently circumscribed tumor with diffuse infiltration into the dermis and subcutis. Grenz zone is characteristically absent. The tumor is made up of fibroblasts arranged in storiform pattern with their nuclei showing mild pleomorphism[95]. Infiltration into the subcutaneous tissue produces a honey comb pattern. Inflammatory cells, giant cells, xanthoma cells are scant or absent.

INFANTILE FIBROSARCOMA:

This tumour is usually well differentiated like adult fibrosarcoma with fasciculated or herring bone growth pattern of tumour cells. Less differentiated medullary type is more cellular and composed of solid sheets of rounded immature cells with hyperchromatic nuclei. Bizarre cells and multinucleated giant cells are rare. Characteristic chronic lymphocytic infiltrate is seen[96,97].

FIBROHISTIOCYTIC TUMOUR :

BENIGN FIBROUS HISTIOCYTOMA:

This tumor is composed of grenz zone beneath epidermal hyperplasia and dermal nodular proliferation of fibroblastic cells arranged in short interlacing fascicles with a vague storiform appearance[98]. Touton type of multinucleated giant cells, chronic lymphocytic infiltrate and xanthoma cells are characteristically seen in BFH.

SMOOTH MUSCLE TUMOUR:

LEIOMYOMA OF DEEP SOFT TISSUE:

Leiomyoma is composed of spindle shaped cells arranged in short intersecting fascicles. Tumour cells have blunt ended elongated nuclei and scanty cytoplasm.

NERVE SHEATH TUMOURS:

NEUROFIBROMA:

Neurofibroma is composed of spindle shaped cells with wavy, buckled dark stained nuclei in a stroma composed of mucoid material, fibroblasts, perineurial cells,mast cells and lymphocytes with variable amount of collagen[65].

SCHWANNOMA:

This is an encapsulated neoplasm composed of both hypercellular Antoni A and hypocellular myxoid Antoni B areas. Antoni A areas are composed of compactly packed spindle cells in short interlacing fascicles and bundles. Tumour cells exhibit peripheral palisading of their nuclei forming Verrocay bodies which are characteristic of Schwannoma. Antoni B areas have scattered oval or spindle cells in a background of loose matrix composed of inflammatory cells and collagen[65].

VASCULAR TUMOURS:

HAEMANGIOMA:

Types include capillary, cavernous, epithelioid haemangiomas and pyogenic granuloma[99]. Capillary haemangiomas are composed of lobules of small capillary sized blood vessels lined by plump endothelial cells. Pyogenic granuloma is

superficial with surface ulceration and marked stromal edema. Cavernous haemangiomas have large dilated vascular spaces with blood filled lumen and lined by flat endothelial cells[100].

Epithelioid haemangioma is also known as angiolymphoid hyperplasia with eosinophilia. It has thin walled blood vessels lined by pale cuboidal endothelial cells with dense collections of eosinophils. Some vessels show tomb like appearance of endothelial cells[101].

KAPOSIFORM HEMANGIOENDOTHELIOMA:

Tumor is composed of multiple irregular nodules infiltrating the deep soft tissue surrounded by desmoplastic stroma. Many glomeruloid structures are seen in the nodules with hyaline droplets, hemosiderin, RBC fragments and fibrin micro thrombi[102].

EPITHELIOID HEMANGIOENDOTHELIOMA:

This tumor is composed of round to spindle shaped endothelial cells arranged in solid nests and short strands. There are no well-formed vascular channels. The tumor cells have intracellular lumen which is seen as vacuoles occasionally containing red blood cells embedded in hyaline to myxoid stroma. These cells are termed as blister cells[103].

KAPOSI SARCOMA:

Late stage of Kaposi sarcoma presents as a nodular lesion in dermis and extend to involve the subcutis. Nodule is composed of proliferation of miniature vessels and spindle shaped tumour cells with little pleomorphism separated by slit like spaces containing red blood cells. Hyaline globules are characteristic. Periphery of the nodule shows lymphoplasmacytic infiltrate and ectatic blood vessels[104].

TUMOUR OF UNCERTAIN DIFFERENTIATION:

ATYPICAL FIBROXANTHOMA:

It is classified as an intermediate and rarely metastasizing soft tissue tumour of uncertain differentiation. Atypical fibroxanthoma involves the dermis of skin with a grenz zone beneath the epidermis. Tumour cells are pleomorphic spindled or large rounded cells with marked nuclear atypia and many typical and atypical mitotic figures[105].

SOFT TISSUE SARCOMAS:

The natural history of sarcomas is highly variable. The histopathological classification is a challenging task. More than 50 subtypes of proliferative soft tissue lesions are defined. Until today, the most common STS diagnosed have been malignant fibrous histiocytoma (now classified as undifferentiated pleomorphic

sarcoma) and liposarcoma which together constitute about 35- 45% of all sarcomas[1]. The classification of STS has not stayed constant over the years, but is regularly re-evaluated and re-formulated. The MFH entity which was introduced 42 years ago by Ozzello et al[106] has been challenged to its mere existence by Fletcher and his coworkers.

The classification is centered on distinct mesenchymal tissues such as fibrous tissue, adipose tissue, muscle, blood vessels, tenosynovial tissue and peripheral nerves. Histologic assessment of soft tissue sarcomas depends on identification of the growth pattern, type of cell lineage along with consideration of the patient's age and sex and the tumour size and location. Many of the tumours still lack clear-cut diagnostic foundation, especially when the tumours exhibit an undifferentiated morphology. Therefore, molecular genetic studies are extremely useful in the clinical evaluation of soft tissue sarcomas.

MORPHOLOGY OF MALIGNANT SOFT TISSUE TUMOURS:

LIPOSARCOMA:

Liposarcomas are of 3 types-

i) Myxoid liposarcoma – composed of small undifferentiated spindle shaped cells and scattered lipoblasts in an abundant mucoid matrix. Characteristic delicate chicken wire like blood vessels seen[109]. Tumour

with increased cellularity and composed of rounded cells with nuclear hyperchromasia is termed as high grade myxoid liposarcoma[107].

ii) Pleomorphic liposarcoma – composed of diffuse sheets of large pleomorphic spindled cells with hyperchromatic nuclei and scattered lipoblasts[108].

iii) Dedifferentiated liposarcoma – composed of areas of well differentiated liposarcoma with sudden or gradual transition to areas of high grade sarcomas with or without lipoblasts, most commonly fibrosarcoma or malignant fibrous histiocytoma[110].

FIBROSARCOMA:

Low grade fibrosarcoma shows spindle shaped cells with mild pleomorphism interspersed with abundant collagen. They are arranged in fascicular or classical Herring bone pattern. High grade fibrosarcomas show less oriented small spindled to rounded cells with marked nuclear atypia and numerous mitoses. Herring bone pattern and collagen are indistinct[111].

SCLEROSING EPITHELIOID FIBROSARCOMA:

Tumour composed of epithelioid cells in a dense sclerotic stroma[112].

MYXOFIBROSARCOMA:

Tumour cells are usually spindle shaped or stellate and seen in a prominent myxoid stroma with characteristic curvilinear branching blood vessels[113].

LOW GRADE FIBROMYXOSARCOMA:

Tumour cells are small spindled with hyperchromatic nuclei seen in alternate fibrous and myxoid areas. Its variant hyalinising spindle cell tumour with giant rosettes has tumour cells forming giant collagenous rosettes in a dense hyalinised stroma[114].

MALIGNANT PERIPHERAL NERVE SHEATH TUMOUR:

MPNST is composed of pleomorphic spindle shaped cells arranged in sheets and fascicles. The cellular fascicles alternate with hypocellular areas giving the tumor a marbled appearance. Well differentiated areas will contain irregular Schwann cells with buckled nuclei. Sub endothelial proliferation of the tumor cells and cartilaginous and osseous metaplasia are also made out[115].

LEIOMYOSARCOMA:

Leiomyosarcomas are usually seen in retroperitoneum and in deep soft tissue of extremities. Cutaneous leiomyosarcomas are uncommon superficial tumours which involve the dermis with extension to subcutaneous tissue[82].

Morphologically, they are characterised by spindle shaped cells with atypical elongated nuclei and eosinophilic cytoplasm arranged in intersecting fascicles and surrounded by deeply eosinophilic myofibrils. Some tumour cells may show paranuclear vacuoles indenting the nuclei. Tumour hypercellularity, marked nuclear atypia with or without mitoses more than or equal to one per 10 HPF are

considered criteria for malignancy. Areas of hyalinization, necrosis and pleomorphic areas with multinucleated giant cells are also can be seen[80].

Variants of leiomyosarcoma include myxoid type, inflammatory type with xanthoma cells and lymphocytes and granular type.

RHABDOMYOSARCOMA:

i) Embryonal Rhabdomyosarcoma is more common in head and neck region followed by genitourinary tract, retroperitoneum and extremities[116]. It is characterized by hypercellular and hypocellular myxoid areas. Tumour cells are small undifferentiated round to oval shaped with hyperchromatic nuclei and indistinct cytoplasm admixed with few or occasional differentiated Rhabdomyoblasts with intense eosinophilic cytoplasm and cross striations. Its variants include spindle cell and botryoid types. Spindle cell variety is seen most commonly in the paratesticular region and resembles leiomyosarcoma. Botryoid type occurs in mucosa lined hollow organs and is characterized by Cambium layer of tumour hypercellularity and a loose myxoid interface between it and the intact epithelium[119].

ii) Alveolar RMS is most commonly seen in the soft tissues of extremities. It is characterized by round to oval shaped tumour cells with hyperchromatic nuclei and scanty cytoplasm arranged in irregular

alveolar pattern. Tumour cells are arranged in a single layer along the hyalinised fibrovascular septa and show central dyscohesion and necrosis. Few rhabdomyoblasts and multinucleated giant cells can be seen[117].

iii) Pleomorphic RMS – common in the soft tissues of extremities. Histologically, it is composed of spindle shaped cells and large pleomorphic rhabdomyoblasts with deep eosinophilic cytoplasm[118].

iv) Sclerosing RMS is characterized by cords, lobules or microalveolar pattern of primitive round cells with hyperchromatic nuclei and indistinct cytoplasm in a densely hyalinised stroma[119].

ANGIOSARCOMA:

These deep soft tissue tumours are composed of sheets and nests of epithelioid tumour cells with high nuclear grade and occasional intracytoplasmic lumen differentiation[120].

MALIGNANT TUMOURS OF UNCERTAIN DIFFERENTIATION:

EXTRASKELETAL EWING'S SARCOMA/ PNET:

In extraskeletal Ewings sarcoma, tumour cells are monomorphic small with uniform round to ovoid nuclei showing fine chromatin and pinpoint nucleoli. Abundant intracytoplasmic glycogen will indent the nuclei[23]. Distinct vascular spaces with necrotic ghost cells consistent with filigree pattern are encountered in

some cases. Rosettes are not common in Ewings sarcoma. Atypical or large cell Ewings' tumour cells have large vesicular nuclei with prominent nucleoli[121].

PNET tumour cells are monomorphic round cells with irregular nuclei showing coarse chromatin and prominent nucleoli. Homer wright rosettes are commonly seen[23].

SYNOVIAL SARCOMA:

Synovial sarcoma is broadly classified into 1.Biphasic type containing both epithelial and spindle cell component in different proportions, 2.spindle cell type and 3.synovial sarcoma not otherwise specified.

Epithelial cells are columnar or cuboidal and are arranged in sheets, nests and glandular pattern. The plump spindle shaped cells are arranged in compact sheets and short fascicles. Cellular portions alternate with hypocellular areas and exhibit areas of hyalinization, calcification and myxoid changes. Presence of mast cells is yet another striking feature of synovial sarcoma[122].

EPITHELIOID SARCOMA:

The tumour cells are arranged in nodular pattern with central degeneration and necrosis. Central necrosis is common. Fusion of necrotizing nodules result in pseudogranulomatous pattern. The cells are large polygonal or oval in shape with

abundant eosinophilic cytoplasm, vesicular nuclei and prominent nucleoli, showing mild pleomorphism. Spindle cell pattern can also be observed[20,21].

'Proximal type' epithelioid sarcoma occurs in axial locations and is characterised by epithelioid tumour cells with marked pleomorphism and show rhabdoid differentiation. Necrosis and pseudogranulomatous pattern are absent[123].

ALVEOLAR SOFT PART SARCOMA:

Morphologically, tumour is composed of cuboidal or polygonal cells with vesicular nuclei and abundant granular eosinophilic cytoplasm arranged in nests and separated by thin sinusoidal vascular septa. Tumour cell nests characteristically show central loss of cellular cohesion resulting in a pseudo alveolar pattern. Mitotic figures are scarce. Vascular invasion can be seen and is a striking finding indicating its metastatic behaviour[124]. PAS stain is of value to demonstrate intracellular cytoplasmic crystalline structures.

EXTRASKELETAL MYXOID CHONDROSARCOMA:

This tumour is composed of cords and sheets of round to elongated tumour cells with small hyperchromatic nuclei and scanty deep eosinophilic cytoplasm seen in an abundant chondroitin sulphate rich mucoid matrix. Tumour has a regular nodular arrangement[22]. Differentiated cartilage cells with lacunae and mitoses are very rare. Areas of haemorrhage are characteristically seen.

UNDIFFERENTIATED/ UNCLASSIFIED TUMOURS:

UNDIFFERENTIATED PLEOMORPHIC SARCOMA:

i) UPS storiform-pleomorphic subtype has storiform areas with well differentiated plump fibroblasts around slit-like vessels, occasional histiocytes and chronic inflammatory cells along with pleomorphic zones with sheets of bizarre tumour cells and rounded histiocytic cells. Mitoses and multinucleated tumour giant cells are common[125].

ii) UPS myxoid subtype has more than 50% myxoid areas with cellular pleomorphic areas[113].

iii) UPS giant cell subtype has nodules of round to spindled cells and osteoclast type giant cells with marked nuclear pleomorphism. Tumour cells are separated by dense fibrovascular bands[125].

iv) UPS inflammatory subtype has benign and malignant rounded xanthoma cells with dense infiltration of neutrophils. Some tumour cells will have phagocytosed neutrophils[125].

DIFFICULTIES IN THE DIAGNOSIS OF STS:

Some benign lesions may mimic sarcomas. For example, nodular and ischaemic fasciitis show zonation effect with hypercellular areas of proliferating fibroblasts surrounding a central hypocellular fibrinoid area[126]. These fibroblasts have vesicular nuclei with prominent nucleoli and sometimes show atypia. Atypical mitotic figures are not usually seen. Sometimes pathologists can stratify a tumour only as sarcoma or non-sarcoma with small biopsy specimens. Hence the precise histopathological classification and diagnosis are not possible with FNA and small biopsy specimens.

Grading is also not precise and often erroneous in small biopsy specimens. Unrepresentative area sampling may lead to the under-diagnosis of low grade sarcoma instead of a high grade sarcoma. Presence of necrosis indicates the possibilities of high grade sarcoma, prior chemotherapy or radiotherapy and previous surgical interventions. Sarcoma necrosis is of coagulative type and should be distinguished from the hyaline change. Grading becomes unreliable in the setting of necrosis due to prior treatment[127]. Hence Immunohistochemistry should be considered whenever possible in cases of suspected soft tissue sarcomas.

IMMUNOHISTOCHEMISTRY:

TABLE 1 - IMMUNOHISTOCHEMICAL MARKERS USED FOR DIAGNOSIS OF SOFT TISSUE TUMOURS[1]:

CELL LINEAGE	USEFUL MARKERS
Myofibroblast	Smooth muscle actins
Epithelial	Cytokeratin (CK), Epithelial Membrane Antigen (EMA)
Skeletal muscle	Desmin, Myogenin, MyoD1, muscle sarcomeric actins
Smooth muscle	Smooth muscle actin (SMA), Caldesmon, Desmin, Myosin heavy chain
Endothelium	CD31, CD34, Factor VIII, Von Willebrand factor, Ulex lectin
Adipocyte	S-100, CDK-4, MDM-2
Melanocyte/ Neural	S-100, HMB-45
Glomus cell	Smooth muscle actin, type 4 collagen

Immunohistochemistry can be used for the diagnosis of a variety of sarcomas such as

- Synovial sarcoma (EMA, CK, Bcl2)
- Epithelioid sarcoma (CD34, CK)
- Clear cell sarcoma (S100, HMB45)
- GIST (CD117, CD34)
- Rhabdomyosarcoma (Desmin,Myogenin, myoD1)
- Epithelioid angiosarcoma (CD31, CD34).

- Leiomyosarcoma (actin +, desmin +/-, caldesmon +/-)
- MPNST (S100 + in 50-60% of cases)
- Dermatofibrosarcoma protuberans (CD34 +)
- Dedifferentiated liposarcoma (MDM2 +, CDK4 +)
- Ewing sarcoma / PNET (CD99, FLI 1)
- CD99 is widely used to recognize small, blue, round cell tumors like poorly differentiated synovial sarcoma and desmoplastic small round cell tumour. FLI-1shows nuclear positivity in only 70% of cases of Ewing sarcoma.
- Fibrosarcomas and undifferentiated pleomorphic sarcomas display no specific marker but immunohistochemistry is helpful to rule out other differentiated sarcomas and non-sarcomas.

GRADING OF SOFT TISSUE SARCOMAS:

- The first grading system for sarcomas was introduced by Broders et al. in 1939 based on degree of cellularity, cellular pleomorphism, mitosis, necrosis, invasive growth, haemorrhage and inflammatory infiltrate[128].
- The FNCLCC grading system was first proposed by Trojani et al in 1984 based on his analysis on 155 cases of soft tissue sarcomas[3]. Grading was based on tumour differentiation, mitotic activity and degree of necrosis.
- FNCLCC grading system was reviewed by Coindre in 2006[154]. Tumor differentiation and mitotic count were given a score from 1-3 and tumor

necrosis was scored as 0-2. The histologic grade is derived from the total score with 2-3 being grade 1, 4-5 being grade 2 and 6-8 being grade 3.

TABLE 2- FNCLCC GRADING SYSTEM OF SARCOMAS[3]

TUMOR DIFFERENTIATION:	
Score 1	Sarcoma with close resemblance to normal adult mesenchymal tissue, eg. well differentiated liposarcoma
Score 2	Sarcoma with certain histologic typing, eg. myxoid liposarcoma
Score 3	Undifferentiated/unclassified sarcomas and sarcomas of unceratin type.
MITOTIC COUNT PER TEN HPF:	
Score 1	0 - 9
Score 2	10 - 19
Score 3	20 or more
TUMOR NECROSIS:	
Score 0	No necrosis
Score 1	less than 50% necrosis
Score 2	50% or more necrosis
Grade 1	Total score 2,3
Grade 2	Total score 4,5
Grade 3	Total score 6,7 and 8

TABLE 3- FNCLCC -TUMOUR DIFFERENTIATION SCORE[3]

HISTOLOGIC TYPE	DIFFERENTIATION SCORE
Well differentiated liposarcoma	1
Myxoid liposarcoma	2
Round cell liposarcoma	3
Pleomorphic liposarcoma	3
Dedifferentiated liposarcoma	3
Well differentiated MPNSTand Fibrosarcoma	1
Conventional MPNST/ and Fibrosarcoma	2
Poorly differentiated MPNST and Fibrosarcma	3
Epithelioid MPNST	3
Malignant triton tumour	3
Well differentiated leiomyosarcoma	1
Conventional leiomyosarcoma	2
Conventional angiosarcoma	2
Poorly differentiated /epithelioid angiosarcoma	3
Undifferentiated sarcomas	3
Sarcomas of uncertain differentiation	3

The NCI grade is derived from the histologic type and histopathological parameters including necrosis, cellularity, pleomorphism and mitosis which was described by Costa et al. in 1984 and modified in 1990[56].

In a comparative study of 410 patients diagnosed with STS, Guillou et al[129] found the FNCLCC grading system to be marginally better at predicting metastasis and disease-specific survival (DSS) compared to the NCI grading system. However, both systems yielded prognostic groups and are recognized in the WHO manual as suitable for grading STSs. In addition to these well recognized systems both two- and four- systems exist.

The three-tiered systems are considered most suitable for predicting survival and likelihood of treatment response, since they are able to predict the behavior of both low-grade, intermediate-grade and high-grade tumors, which seem to be well defined categories of STSs. SIN system proposed by the SSG group anticipated promising binary stratification which would help to simplify treatment strategy scheme[130]. The system uses three factors, namely Size, vascular Invasion and Necrosis in a dichotomous fashion (size < or > 8 cm, and +/– vascular invasion and necrosis). The low risk group (score 0-1) had an 81% 5-year survival compared to the high-risk group (score 2-3) with a 5-year survival of 32%[130].

STAGING:

STSs are typically staged according to TNGM system devised by Russel et al. in 1977[24]. This was later revised and currently published in the AJCC Cancer Staging Manual 7th edition. The TNGM system for STSs includes tumor size,

nodal metastasis, malignancy grade and distant metastasis to give a stage ranging from I-IV.

TABLE 4: STAGING OF SARCOMAS

Stage	Tumor	Node	Metastasis	Grade	Definition
Ia	T1a	N0	M0	G1, GX	T1: Tumor ≤5cm in greatest
	T1b	N0	M0	G1, GX	dimension
Ib	T2a	N0	M0	G1, GX	T1a: Superficial tumor
	T2b	N0	M0	G1, GX	T1b: Deep tumor
IIa	T1a	N0	M0	G2, G3	T2: Tumor>5cm in greatest
	T1b	N0	M0	G2, G3	dimension
IIb	T2a	N0	M0	G2	T2a: Superficial tumor
	T2b	N0	M0	G2	T2b: Deep tumor
III	T2a, T2b	N0	M0	G3	N1: Regional lymph node
	Any T	N1	M0	Any G	metastasis
IV	Any T	Any N	M1	Any G	M1: Distant metastsis
					G: Histological grade

In 2002, Kattan et al. published the Memorial Sloan-Kettering Cancer Center (MSKCC) system in which they utilized a subset of independent prognostic markers to predict the clinical cancer development[131]. This approach has later been adapted for several clinical situations (pre-/post-operative, after recurrence etc.) and for specific subsets of patients. If developed and used correctly, these

nomograms seem to be better able to predict the clinical course of the individual patient than the conventional staging systems.

VASCULAR INVASION IN STS:

In STS, vascular invasion is generally not applied systematically in pathological evaluations. However, it is considered as one of three major prognostic factors in the SIN (Size, vascular Invasion and Necrosis) system, elaborated by Scandinavian Sarcoma Group (SSG). By SSG designation, vascular invasion can be defined as the presence of tumor cells within any space lined by endothelial cells. These tumour cells can be either attached to the vessel wall or free floating along with fibrin, RBCs and WBCs[130].

OTHER PROGNOSTICATORS IN STS:

Primary tumor location has been previously reported as an important prognostic marker in STS, with head and neck as well as retroperitoneal location greatly increasing STS specific mortality. Several studies suggest that margin status of positivity is a marker of adverse prognosis. For example, the MSKCC group (2002)[131] reported 1.6 fold increased risk of death in sarcomas with margin positivity. In another analysis, 2.9- fold increased risk of sarcoma death is reported.

Other clinical factors reported as a prognosticator in STS include local and distant recurrence, and nodal status.

MOLECULAR PROGNOSTIC MARKER KI 67:

The Ki-67 antigen was identified as a protein of nuclear origin associated with cellular proliferation in 1983[4]. It is expressed during the proliferating phases of the cell cycle (Gerdes et al, 1984)[4]. It is a sensitive proliferation marker when compared to mitotic index because it recognizes late G1, S1, M and G2 phases of cell cycle except G0. Ki-67 has been proved to be a reliable marker for cell growth measurement in human neoplasms[135] (Brown et al, 1990). Immunostaining of formalin-fixed paraffin embedded (FFPE) material was possible with the help of MIB-1 antibody[137] (Gerdes et al 1992) and microwave antigen retrieval technique[133] (Shi et al 1991). FFPE material stained with MIB-1 and fresh tissue stained with Ki-67 had a good correlation[132] (Cattoretti et al, 1992). Heslin et al, 1998 on his study on primary high-grade sarcomas recognized Ki-67 as an independent prognostic marker[10]. Similarly, study on angiosarcoma with Ki-67 proved prognostic significance of Ki-67[120] (Meis-Kindblom et al, 1998) but this result was not obtained in a study with MFH[136] (Zehr et al, 1990).

Ki67 cut-off value varied from 10% (Choong et al, 1995)[5] to 40% (Levine et al, 1997)[7] for sarcomas. Ki-67 proliferative index was defined as the percentage of tumor cells showing nuclear positivity with a reference cutoff value of 20–40%. Various studies had revealed the positive correlation between high Ki-67 proliferative index and poor overall outcome in sarcoma patients. High Ki-67

proliferative index can be useful in the selection of high risk sarcomas for systemic adjuvant chemotherapy or radiotherapy to provide metastasis free survival and low Ki-67 index can be used to avoid overtreatment and aggressive side effects of the adjuvant therapy.

Hence Ki-67 index should be used in the grading and staging systems for clinical evaluation of soft tissue sarcomas.

MATERIALS AND METHODS

MATERIALS AND METHODS

STUDY DESIGN

The present study was a prospective study conducted at the Department of Pathology, Madurai medical college during the period of July 2014 to July 2016. Ethical clearance for the study was obtained from the Ethical Committee of Madurai medical college, Madurai.

A total sample of 100 cases of soft tissue tumors, including both benign and malignant tumors, was analyzed during this period.

INCLUSION CRITERIA

Resected specimens and excision biopsy specimens of clinically and radiologically suspected soft tissue tumors.

EXCLUSION CRITERIA

- Incisional biopsy specimens of soft tissue tumours
- Lipomas were excluded.
- Resected specimens of soft tissue tumours modified by neo-adjuvant chemotherapy or radiotherapy.

METHODOLOGY AND TECHNIQUES

The study material included 100 soft tissue tumours. (Annexure VA)

Clinical and morphological details of cases were recorded according to the proforma (Annexure II)

Operated resection specimens were collected and fixed in 10% neutral buffered formalin for 12 hours.

After adequate fixation, the specimens were photographed and sliced with 5–10 mm intervals. The percentage of gross necrosis was estimated. The margins were best evaluated by sections taken perpendicular to the specimen surface closest to the tumor. Representative bits were taken from the tumour, adjacent soft tissue, surgical margins and lymph nodes. They were processed routinely and multiple 4 to 6 micron thin paraffin sections were obtained.

Staining was done by Hematoxylin and Eosin staining technique (Annexure III)

HISTOMORPHOLOGICAL EVALUATION:

Stained slides were evaluated under light microscopic examination. Tumours were classified as benign or malignant based on cellularity, nuclear atypia and presence or absence of atypical mitotic figures. Tumours were categorized broadly according to their pattern of differentiation. (Annexure VA)

Malignant soft tissue sarcomas were further analyzed and histologically graded using the FNLCC (Federation Nationale des Centres de Lutte Contre Le Cancer) grading system (Tables 1 and 2) which included assessment of tumour

differentiation score, mitotic count per 10 high power fields and tumour necrosis volume. (Annexure VB)

IMMUNOHISTOCHEMICAL EVALUATION:

Selected cases of soft tissue sarcomas were subjected to Immunohistochemical evaluation with proliferative marker Ki-67 using the monoclonal antibody MIB-1. High density stained areas of the tumour were selected. Diffuse or granular nuclear staining of the tumour cells irrespective of the intensity of staining was taken as Ki-67 positivity. About 500 to 1000 cells were counted in ten high power fields (400X magnification) and converted into percentage. Ki-67 score and labeling index were evaluated for soft tissue sarcomas as follows:

PERCENTAGE OF POSITIVE TUMOUR NUCLEI	KI-67 SCORE	KI-67 INDEX
1-25%	1	LOW
26-50%	2	HIGH
>50%	3	HIGH

STATISTICAL ANALYSIS

Data obtained was entered into Microsoft excel spread sheet. The data was analyzed using ratios and percentage. Spearman's Rho and Pearman's Coefficient correlation studies were done to assess the strength of correlation between histologic grade and Ki-67 index. p value was derived to determine the statistical significance level of the study. Observations and results were compared with other studies and inferences drawn.

OBSERVATION AND RESULTS

OBSERVATION AND RESULTS

A total sample of 100 cases of Soft tissue tumours, including both benign and malignant tumors, was analyzed during the study period. The total number of neoplasms diagnosed during the same period was 7750. Hence, soft tissue tumours constituted only about 1.3% of all neoplasms. (Chart 1)

CHART 1- OVERALL INCIDENCE OF SOFT TISSUE TUMOURS

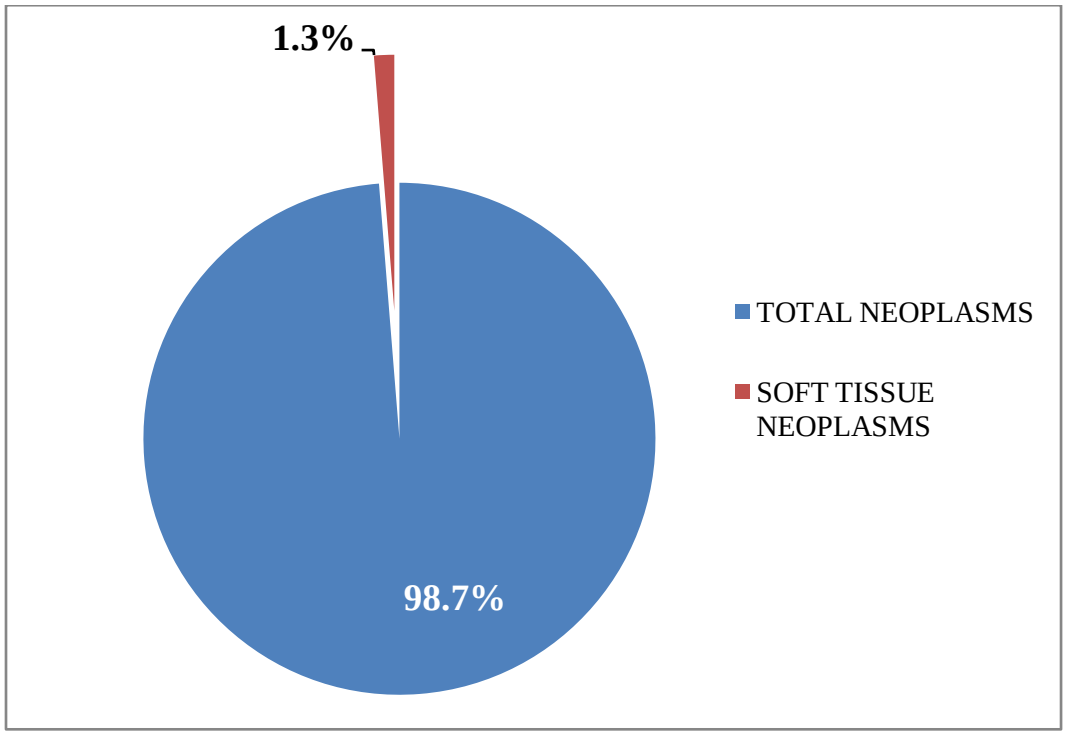
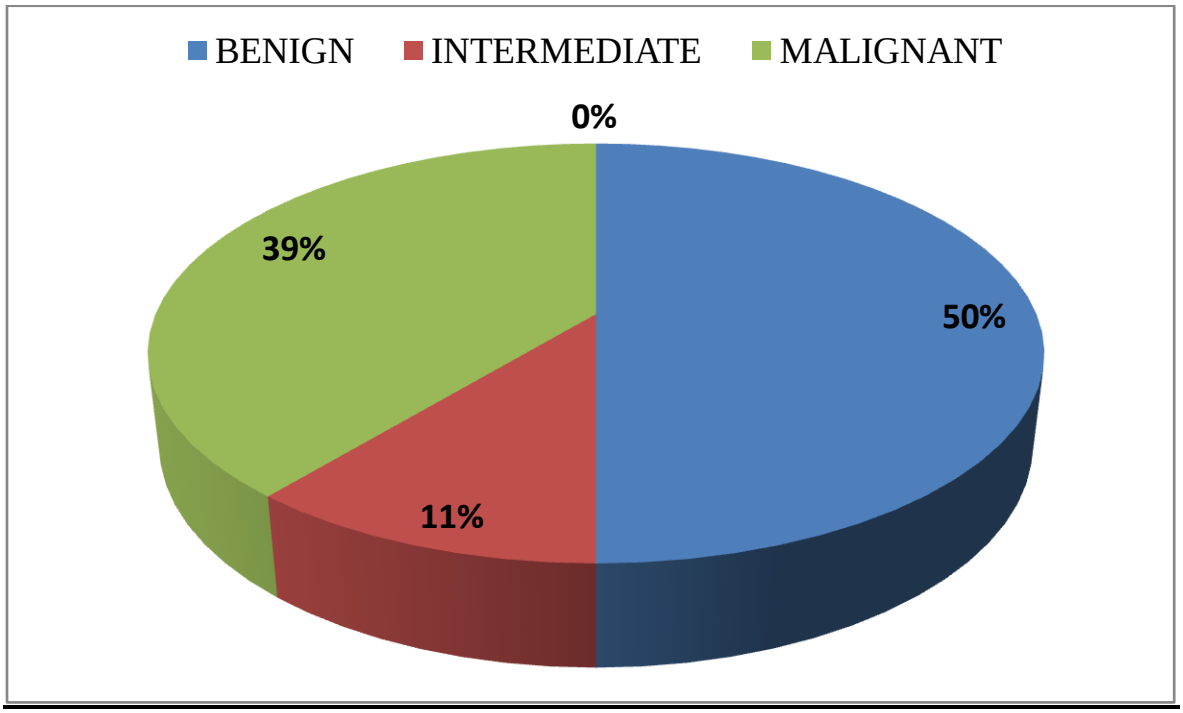


TABLE 5: CLASSIFICATION OF STT BASED ON THEIR BEHAVIOUR

TYPE	DISTRIBUTION	
	FREQUENCY	PERCENTAGE
BENIGN	50	50%
INTERMEDIATE	11	11%
MALIGNANT	39	39%
TOTAL	100	100%

CHART 2- DISTRIBUTION OF TUMORS ACCORDING TO BEHAVIOUR



In the present study, majority of soft tissue tumours were benign constituting about 50%, followed by malignant tumours with 39% and intermediate grade tumours forming the least group with 11 %.(Table 5 and chart 2)

TABLE 6- AGE WISE DISTRIBUTION OF STT

AGE GROUP	NUMBER	PERCENTAGE
< 10 Years	4	4%
10-19 Years	6	6%
20 – 29 Years	17	17%
30 -39 Years	12	12%
40 – 49 Years	22	22%
50 – 59 Years	23	23%
> 60 Years	16	16%
TOTAL	100	100%

In the present study, the age range was 1 to 80 years with mean age of 42.11 years and median age of 45 years. Majority of soft tissue tumours occurred in the age

group of 50-59 years (23%), followed by 40-49 years age group (22%) and the least number of tumours occurred in the age group of <10 years (4%). (Table 6 and chart 3)

CHART 3- AGE-WISE DISTRIBUTION OF SOFT TISSUE TUMORS

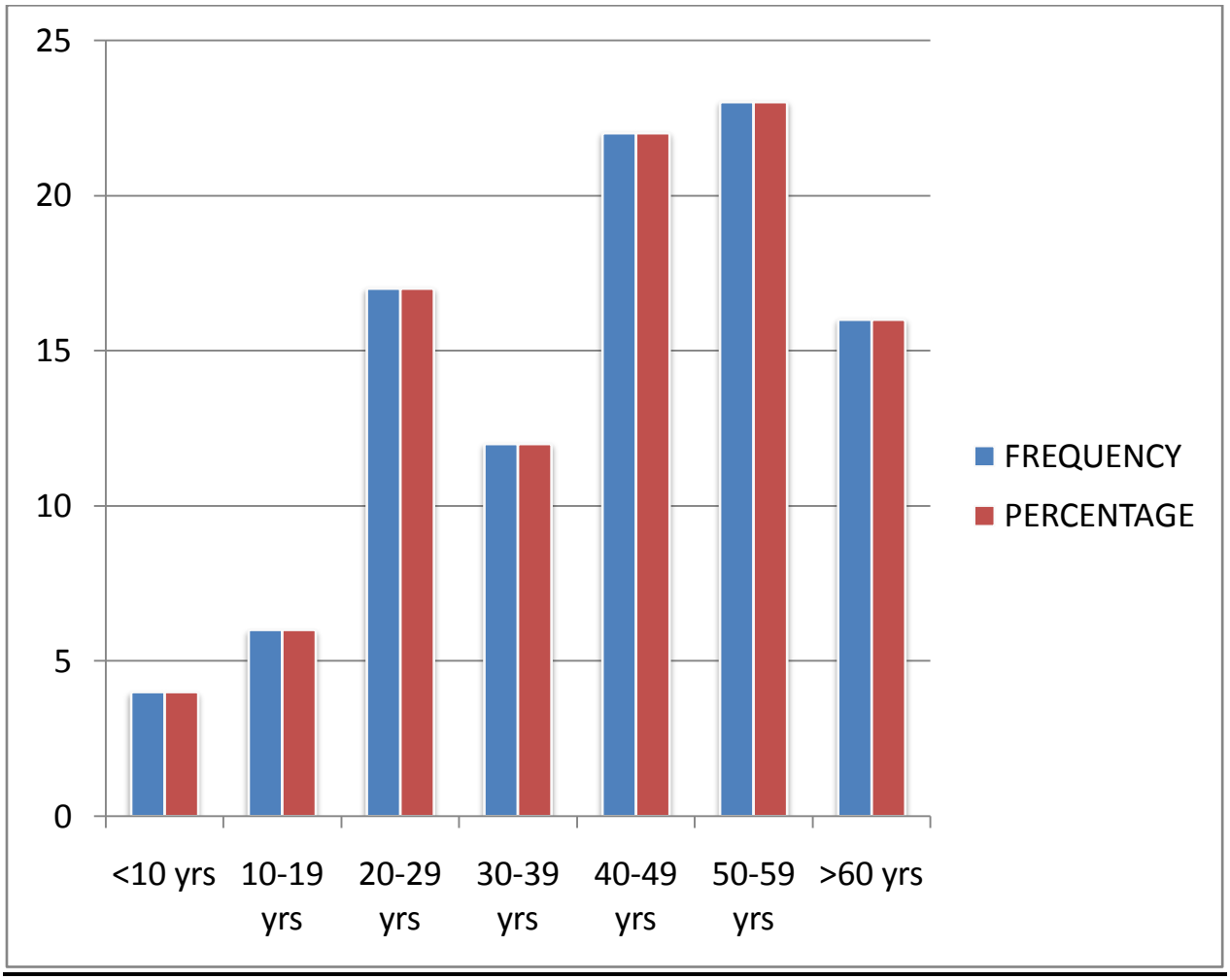


TABLE 7: SEX-WISE DISTRIBUTION OF STT

GENDER	NUMBER	PERCENTAGE
MALE	52	52%
FEMALE	48	48%
TOTAL	100	100%

In the present study, male to female ratio was 1:0.9 indicating that the incidence of soft tissue tumours was slightly higher in male gender. (Table 7 and chart 4)

CHART 4- SEX-WISE DISTRIBUTION OF SOFT TISSUE TUMOURS

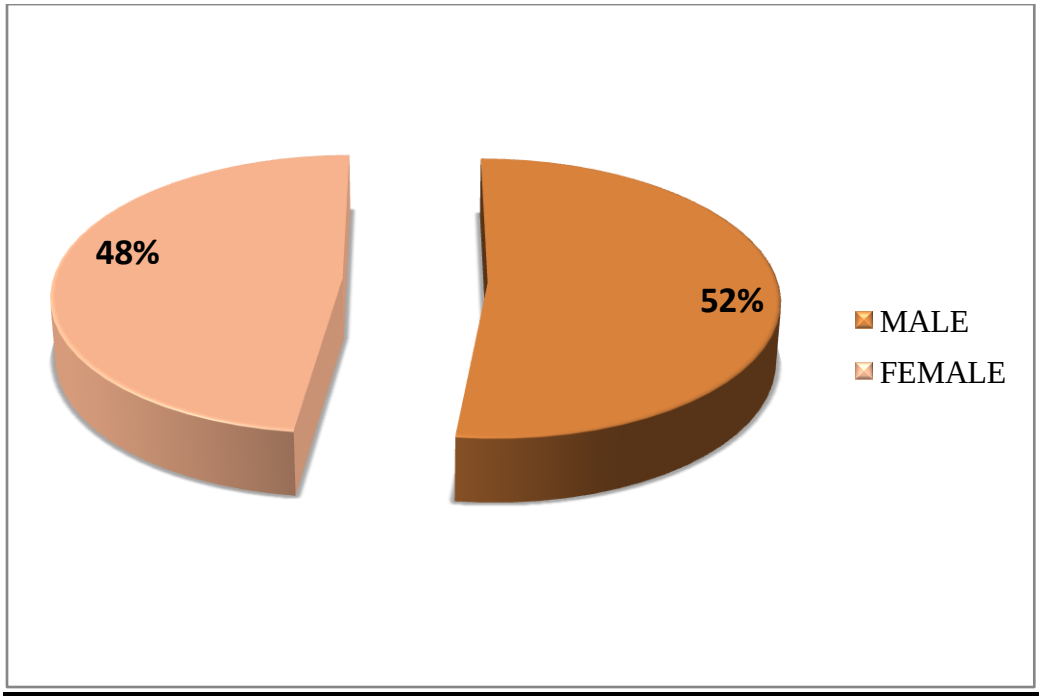


TABLE 8: DISTRIBUTION OF STT ACCORDING TO SITE

SITE	FREQUENCY	PERCENTAGE
HEAD & NECK	14	14%
UPPER EXTREMITY	25	25%
LOWER EXTREMITY	32	32%
ABDOMEN	13	13%
THORAX	6	6%
BACK	10	10%
TOTAL	100	100%

Table 8 shows the anatomic distribution of soft tissue tumours in the present study.

Most of the soft tissue tumours involved the lower extremity in about 32% of cases followed by 25% cases in upper extremity and 14% cases in head and neck region. Least common site involved was thorax (6%). The site of predilection was upper extremities for benign tumours and lower extremities for malignant soft tissue tumours.

CHART 5 - DISTRIBUTION OF TUMORS ACCORDING TO SITE

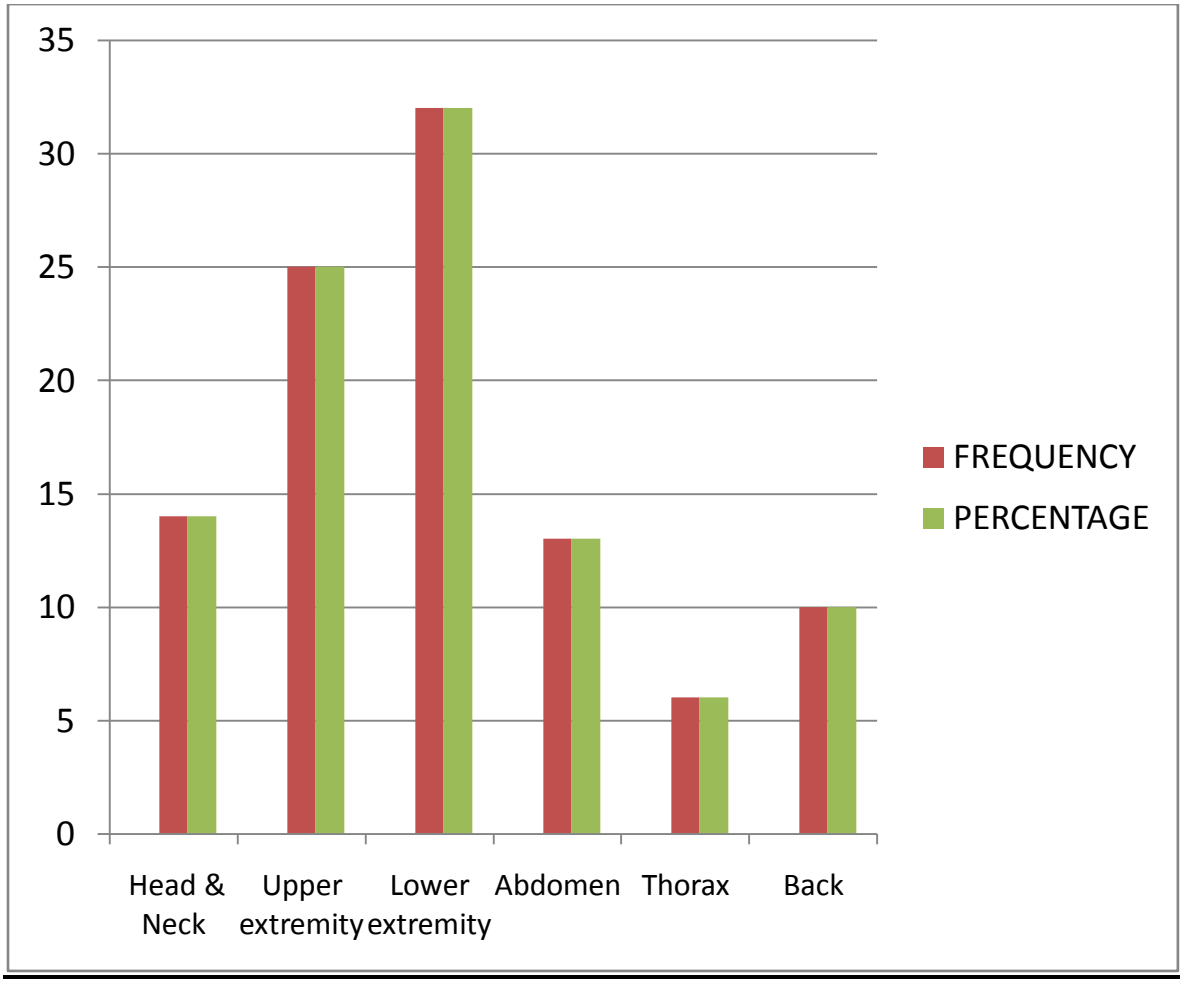


TABLE 9: OVERALL DISTRIBUTION OF SOFT TISSUE TUMOURS

TUMOR	NUMBER	PERCENTAGE
ADIPOCYTIC TUMOR	11	11%
FIBROBLASTIC/MYOFIBROBLASTIC TUMOR	15	15%
FIBROHISTIOCYTIC TUMOR	5	5%
VASCULAR TUMOR	6	6%
PERIVASCULAR TUMOR	1	1%
NERVE SHEATH TUMOR	36	36%
SMOOTH MUSCLE TUMOR	4	4%
SKELETAL MUSCLE TUMOR	1	1%
TUMOR OF UNCERTAIN DIFFERENTIATION	10	10%
UNDIFFERENTIATED TUMOR	11	11%
TOTAL	100	100%

The most common soft tissue tumours in our study were nerve sheath tumours constituting about 36%. Next common tumours were fibroblastic/myofibroblastic

tumours (15%), adipocytic and undifferentiated soft tissue tumours (11% each). The least common soft tissue tumours constituting about 1% were skeletal muscle and pericytic tumours. (Table 9 and chart 6)

CHART 6 - OVERALL DISTRIBUTION OF STT

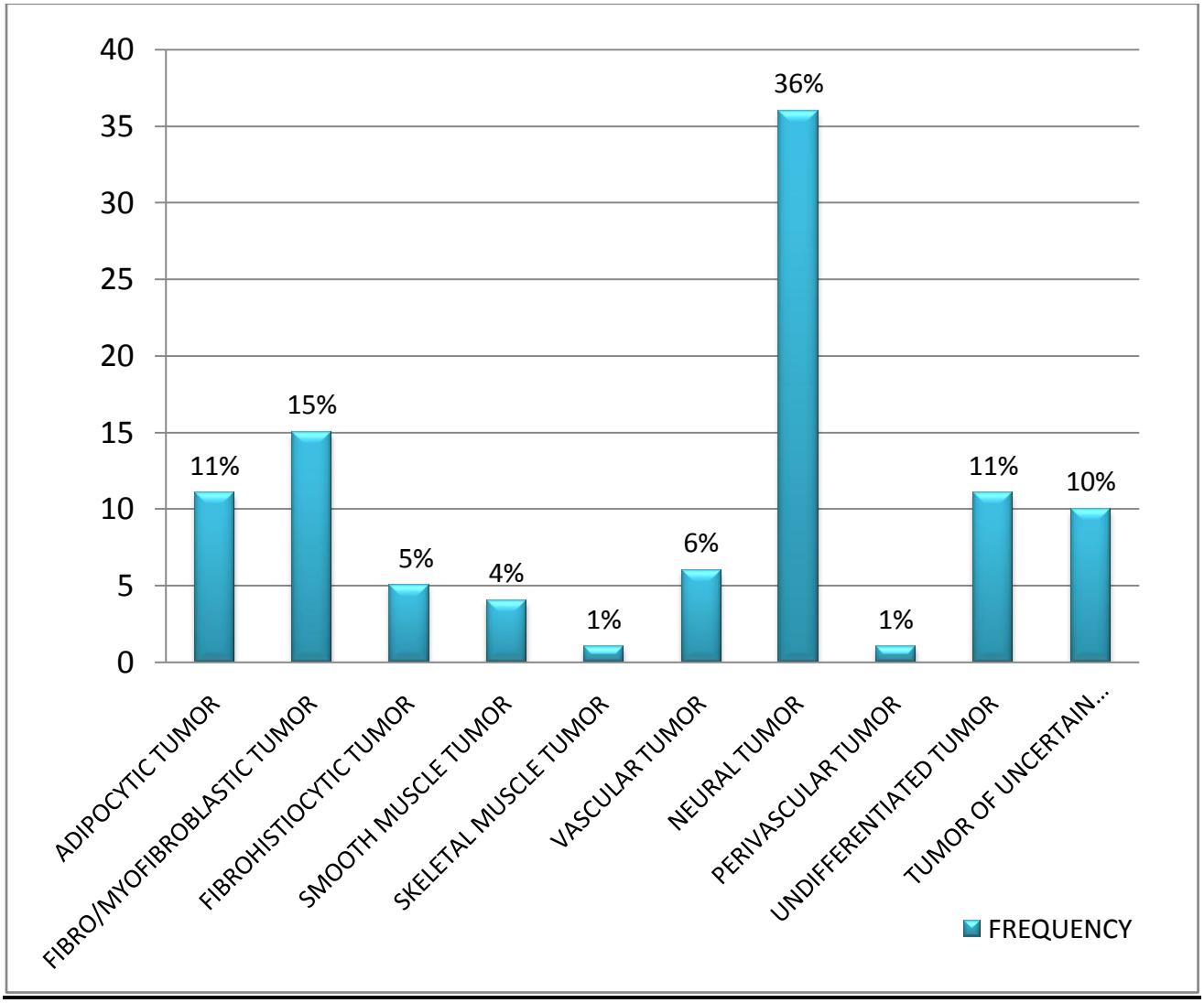


TABLE 10 - DISTRIBUTION OF SOFT TISSUE TUMORS ACCORDING TO WHO CLASSIFICATION

TUMOUR TYPE		NUMBER	PERCENTAGE
ADIPOCYTIC TUMOURS	PLEOMORPHIC LIPOMA	1	1%
	WELL DIFFERENTIATED LIPOSARCOMA	3	3%
	MYXOID LIPOSARCOMA	4	4%
	DEDIFFERENTIATED LIPOSARCOMA	3	3%
	TOTAL	11	11%
FIBRO/MYOFIBRO-BLASTIC TUMOURS	FIBROMATOSIS	2	2%
	GIANT CELL FIBROBLASTOMA	1	1%
	JUVENILE HYALINE FIBROMATOSIS	1	1%
	DERMATOFIBROSARCOMA PROTUBERANS	4	4%
	FIBROSARCOMA	6	6%
	INFANTILE FIBROSARCOMA	1	1%
	TOTAL	15	15%
FIBROHISTIOCYTIC TUMOURS	BENIGN FIBROUS HISTIOCYTOMA	5	5%

VASCULAR TUMOURS	HAEMANGIOMA	6	6%
SMOOTH MUSCLE TUMOURS	LEIOMYOMA	2	2%
	LEIOMYOSARCOMA	2	2%
	TOTAL	4	4%
SKELETAL MUSCLE TUMOURS	ALVEOLAR RHABDOMYOSARCOMA	1	1%
PERIVASCULAR TUMOURS	GLOMANGIOMA	1	1%
NERVE SHEATH TUMOURS	NEUROFIBROMA	19	19%
	SCHWANNOMA	14	14%
	MALIGNANT PERIPHERAL NERVE SHEATH TUMOUR	3	3%
	TOTAL	36	36%
UNDIFFERENTIATED TUMOURS	UNDIFFERENTIATED PLEOMORPHIC SARCOMA	11	11%
TUMOURS OF UNCERTAIN DIFFERENTIATION	MYXOMA	1	1%
	SYNOVIAL SARCOMA	7	7%
	ALVEOLAR SOFT PART SARCOMA	1	1%
	EXTRASKELETAL MYXOID CHONDROSARCOMA	1	1%
	TOTAL	10	10%

Table 10 analyses the distribution of soft tissue tumours according to WHO classification. Nerve sheath tumours (36%) were the most common comprising of 19% neurofibromas, 14% schwannomas and 3% malignant peripheral nerve sheath tumours. Fibroblastic tumours (15%) were the second most common tumours with 6% of them contributed by fibrosarcomas. Undifferentiated pleomorphic sarcomas and adipocytic tumours constituted about 11% of soft tissue tumours in the present study.

TABLE 11- HISTOPATHOLOGICAL CLASSIFICATION OF BENIGN SOFT TISSUE TUMOURS

DIAGNOSIS	NUMBER	PERCENTAGE
PLEOMORPHIC LIPOMA	1	2%
JUVENILE HYALINE FIBROMATOSIS	1	2%
BENIGN FIBROUS HISTIOCYTOMA	5	10%
HAEMANGIOMA	6	12%
NEUROFIBROMA	19	38%
SCHWANNOMA	14	28%
LEIOMYOMA	2	4%
GLOMANGIOMA	1	2%
MYXOMA	1	2%
TOTAL	50	100%

In the present study, Neurofibroma was the most common benign soft tissue tumour diagnosed (38%) followed by Schwannoma (28%) and Haemangioma (12%). The least common benign soft tissue tumours comprising about 2% each were pleomorphic lipoma, juvenile hyaline fibromatosis, glomangioma and myxoma. (Table 11 and chart 7)

CHART 7- HISTOPATHOLOGICAL CLASSIFICATION OF BENIGN SOFT TISSUE TUMOURS

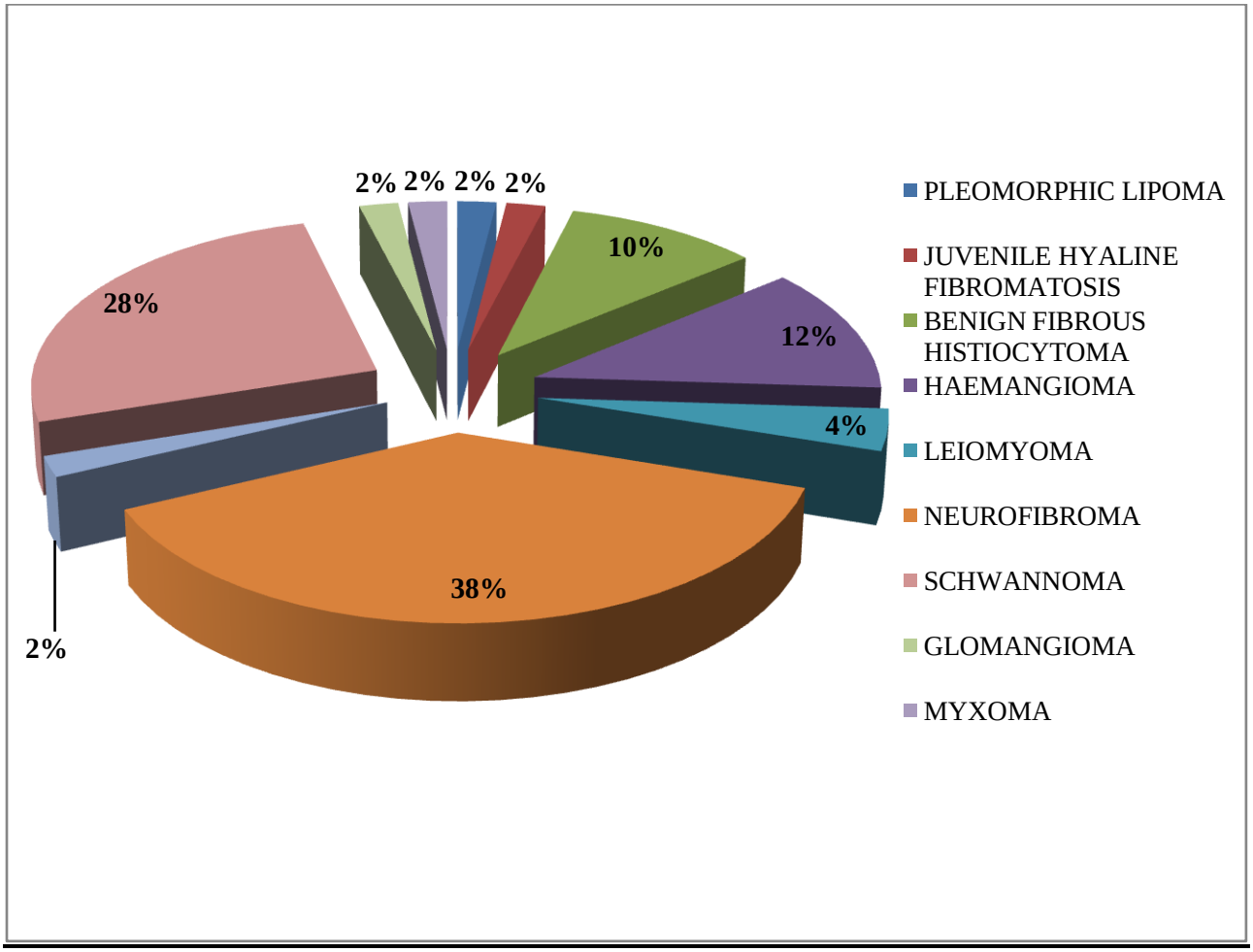


TABLE 12 - AGE AND SEX WISE DISTRIBUTION OF BENIGN SOFT TISSUE TUMOURS

AGE GROUP	MALES		FEMALES		TOTAL
	NUMBER	PERCENTAGE	NUMBER	PERCENTAGE	
<10 years	1	4	1	4	2
10-19 years	3	12	2	8	5
20-29 years	8	32	7	28	15
30-39 years	3	12	3	12	6
40-49 years	5	20	8	32	13
50-59 years	5	20	2	8	7
60-69 years	0	0	2	8	2
TOTAL	25	100%	25	100%	50

In the present study, the incidence of benign soft tissue tumours was equal in both males and females with ratio of 1:1. Benign soft tissue tumours were common in the age group of 20-29 years in males and 40-49 years in females constituting about 32% each. (Table 12 and chart 8)

CHART 8- AGE AND SEXWISE DISTRIBUTION OF BENIGN STT

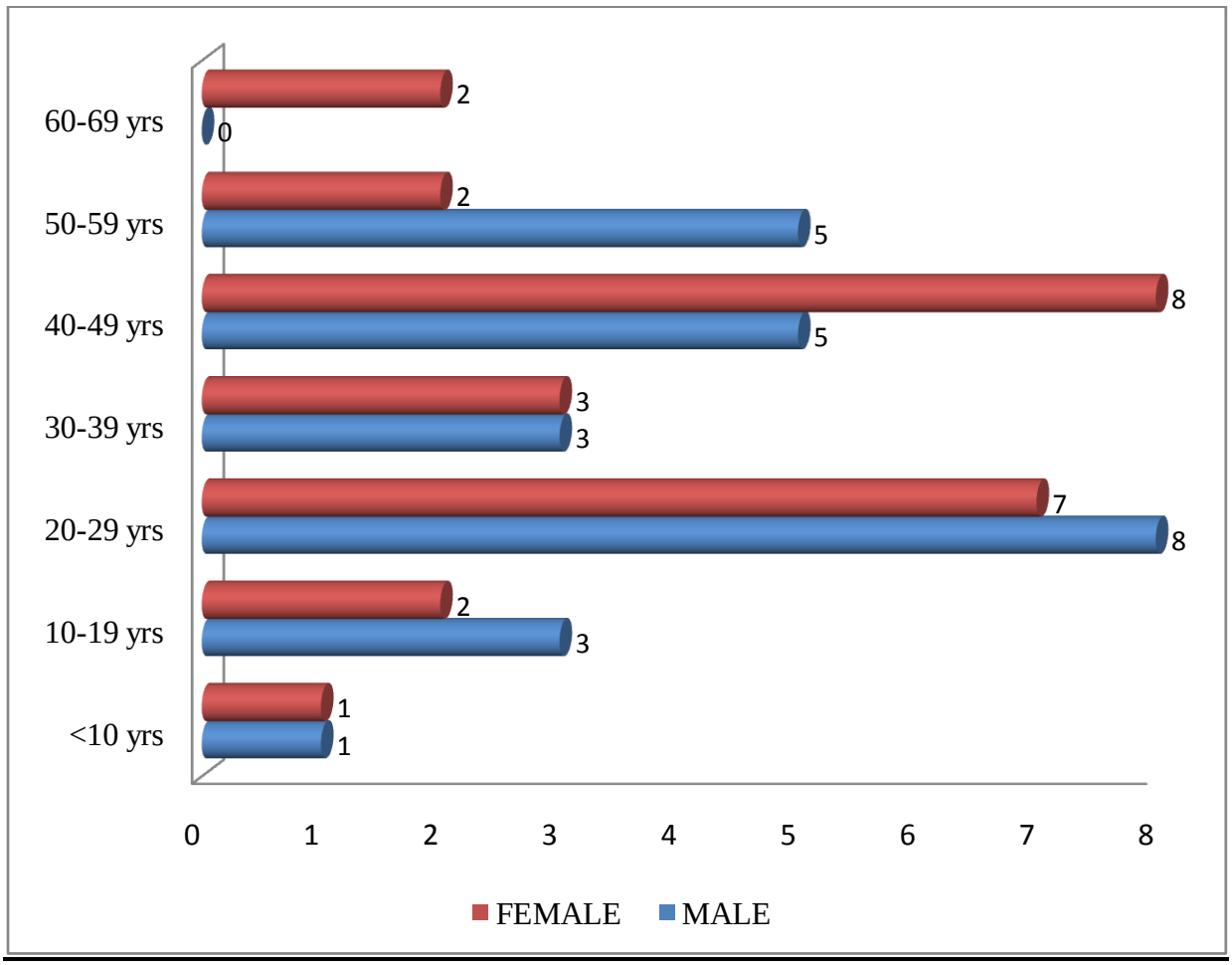
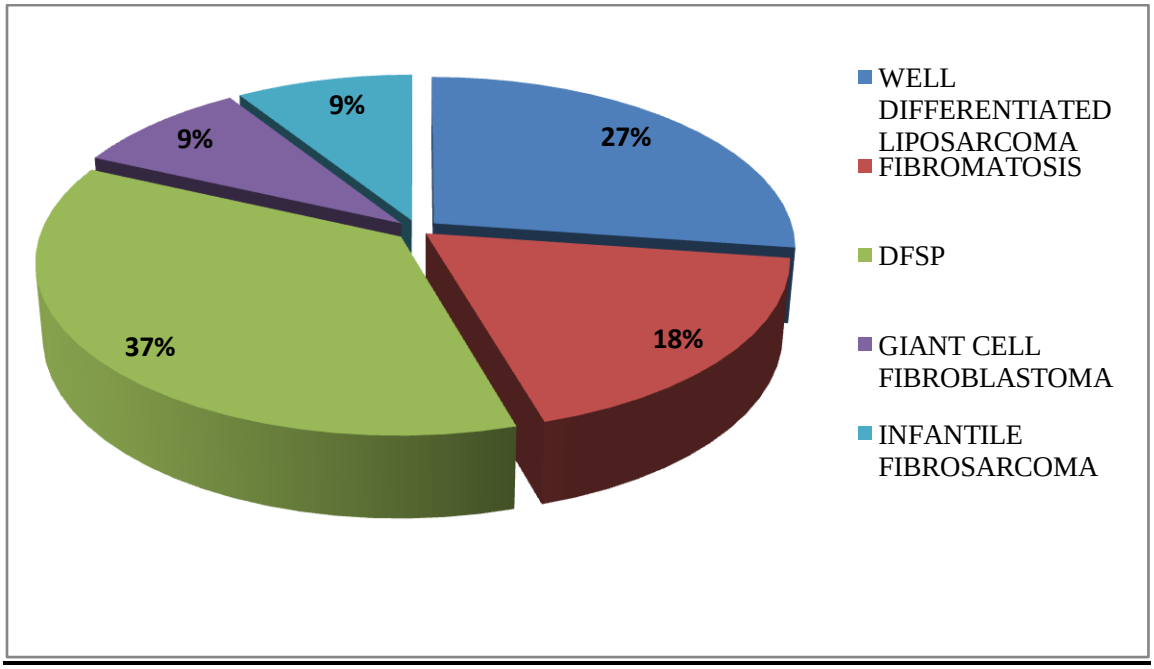


TABLE 13- HISTOPATHOLOGICAL CLASSIFICATION OF INTERMEDIATE SOFT TISSUE TUMOURS

DIAGNOSIS	NUMBER	PERCENTAGE
WELL DIFFERENTIATED LIPOSARCOMA	3	27%
FIBROMATOSIS	2	18%
DFSP	4	37%
GIANT CELL FIBROBLASTOMA	1	9%
INFANTILE FIBROSARCOMA	1	9%
TOTAL	11	100%

CHART 9 - HISTOPATHOLOGICAL CLASSIFICATION OF INTERMEDIATE SOFT TISSUE TUMOURS



In the present study, the most common intermediate soft tissue tumours were Dermatofibrosarcoma protuberans (37%) followed by Well differentiated liposarcoma / atypical lipomatous neoplasm (27%). (Table 13 and chart 9)

TABLE 14 – AGE AND SEXWISE DISTRIBUTION OF INTERMEDIATE SOFT TISSUE TUMOURS

AGE GROUP	MALES		FEMALES		TOTAL
	NUMBER	PERCENTAGE	NUMBER	PERCENTAGE	
<10 yrs	2	33.33	0	0	2
10—19 yrs	0	0	0	0	0
20-29 yrs	0	0	0	0	0
30-39 yrs	1	16.67	1	20	2
40-49 yrs	1	16.67	0	0	1
50-59 yrs	0	0	3	60	3
60-69 yrs	1	16.67	1	20	2
70-79 yrs	1	16.67	0	0	1
TOTAL	6	100%	5	100%	11

In the present study, intermediate soft tissue tumours were common in males with male to female ratio of 1.2:1. Among males, 33.33 % of cases occurred in the first decade. Among females, 60% of cases occurred in the sixth decade. (Table 14 and chart 10)

CHART 10 – AGE AND SEXWISE DISTRIBUTION OF INTERMEDIATE SOFT TISSUE TUMOURS

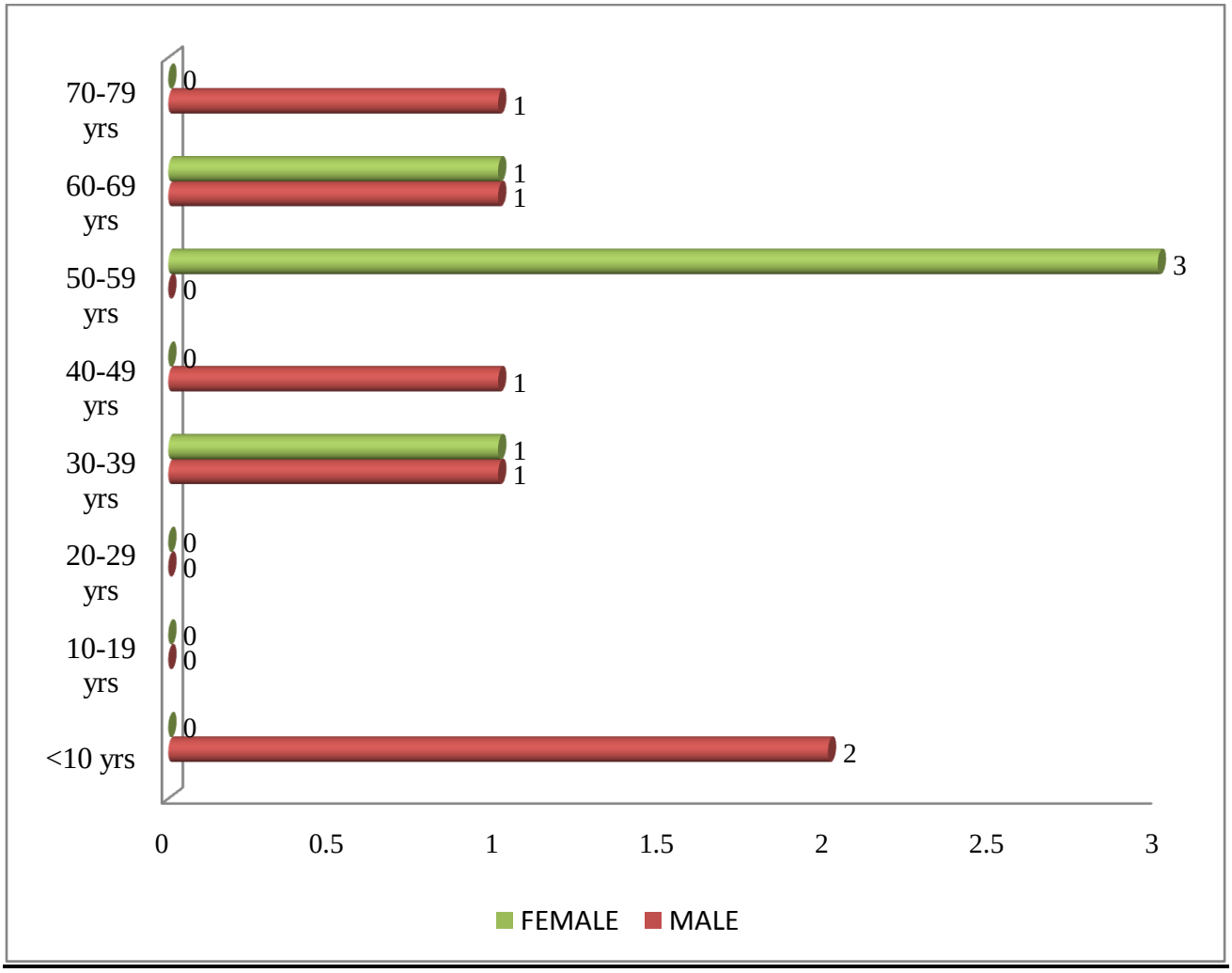


TABLE 15- HISTOPATHOLOGICAL CLASSIFICATION OF MALIGNANT SOFT TISSUE TUMOURS

DIAGNOSIS	NUMBER	PERCENTAGE
MYXOID LIPOSARCOMA	4	10.25%
DEDIFFERENTIATED LIPOSARCOMA	3	7.70%
FIBROSARCOMA	6	15.38%
ALVEOLAR RHABDOMYOSARCOMA	1	2.56%
LEIOMYOSARCOMA	2	5.13%
MPNST	3	7.70%
SYNOVIAL SARCOMA	7	17.94%
ALVEOLAR SOFT PART SARCOMA	1	2.56%
EXTRASKELETAL MYXOID CHONDROSARCOMA	1	2.56%
UNDIFFERENTIATED PLEOMORPHIC SARCOMA	11	28.20%
TOTAL	39	100%

In the present study, the most common malignant soft tissue tumour constituting about 28.20% was Undifferentiated pleomorphic sarcoma followed by Liposarcoma and Synovial sarcoma (17.95% each) (Table 15 and chart 11)

CHART 11- HISTOPATHOLOGICAL CLASSIFICATION OF MALIGNANT SOFT TISSUE TUMOURS

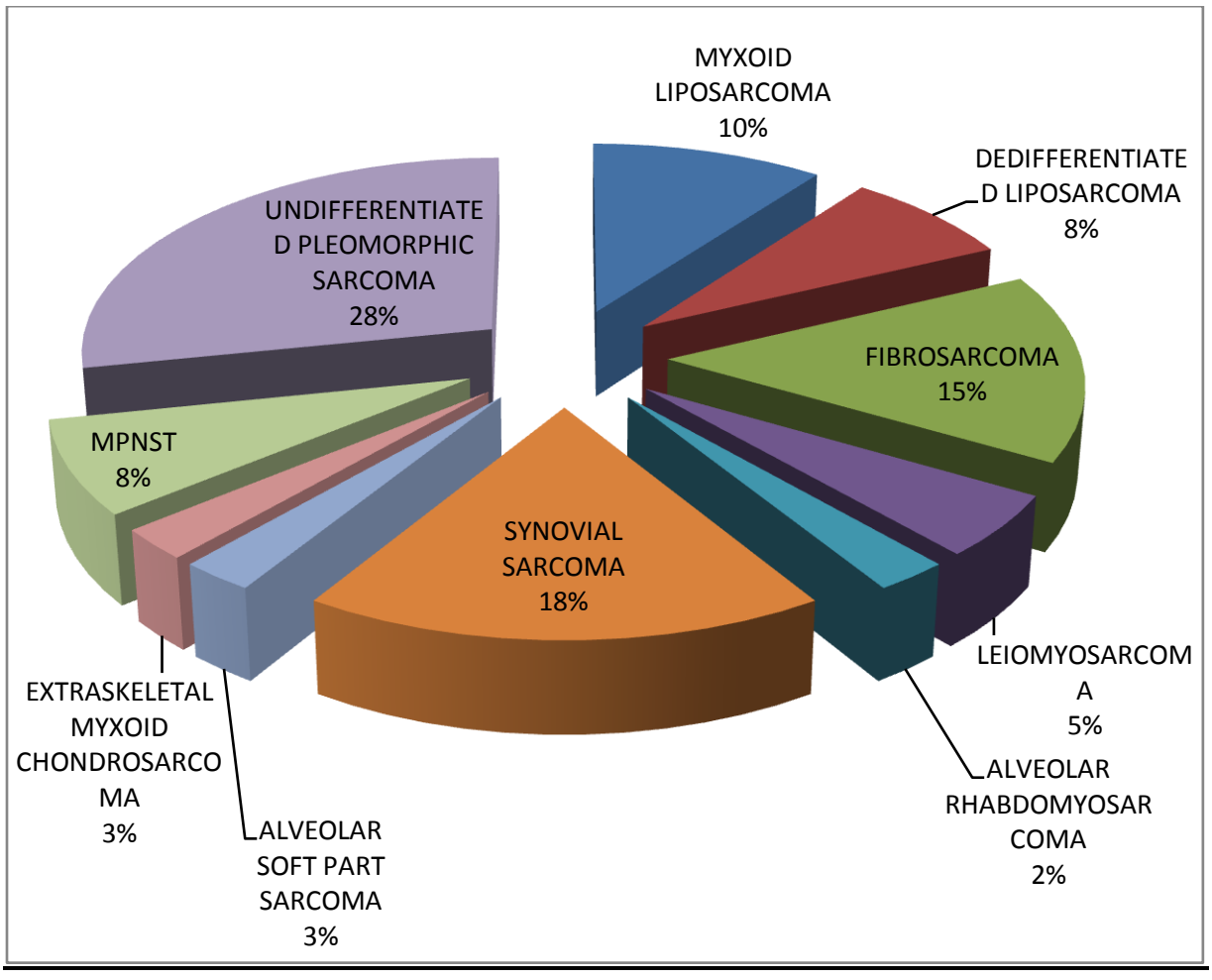


TABLE 16- AGE AND SEXWISE DISTRIBUTION OF MALIGNANT SOFT TISSUE TUMOURS

AGE GROUP	MALES		FEMALES		TOTAL
	NUMBER	PERCENTAGE	NUMBER	PERCENTAGE	
<10 yrs	0	0	0	0	0
10—19 yrs	0	0	1	5.56	1
20-29 yrs	0	0	2	11.11	2
30-39 yrs	3	14.28	1	5.56	4
40-49 yrs	4	19.05	4	22.22	8
50-59 yrs	7	33.33	6	33.33	13
60-69 yrs	4	19.05	2	11.11	6
70-79 yrs	2	9.52	2	11.11	4
80-89 yrs	1	4.76	0	0	1
TOTAL	21	100%	18	100%	39

In the present study, malignant soft tissue tumours were common in males with male to female ratio of 1.2:1. Malignant soft tissue tumours were common in the sixth decade (50-59 years) constituting about 33.33% of cases in both males and females. (Table 16)

CHART 12- AGE AND SEXWISE DISTRIBUTION OF MALIGNANT SOFT TISSUE TUMOURS

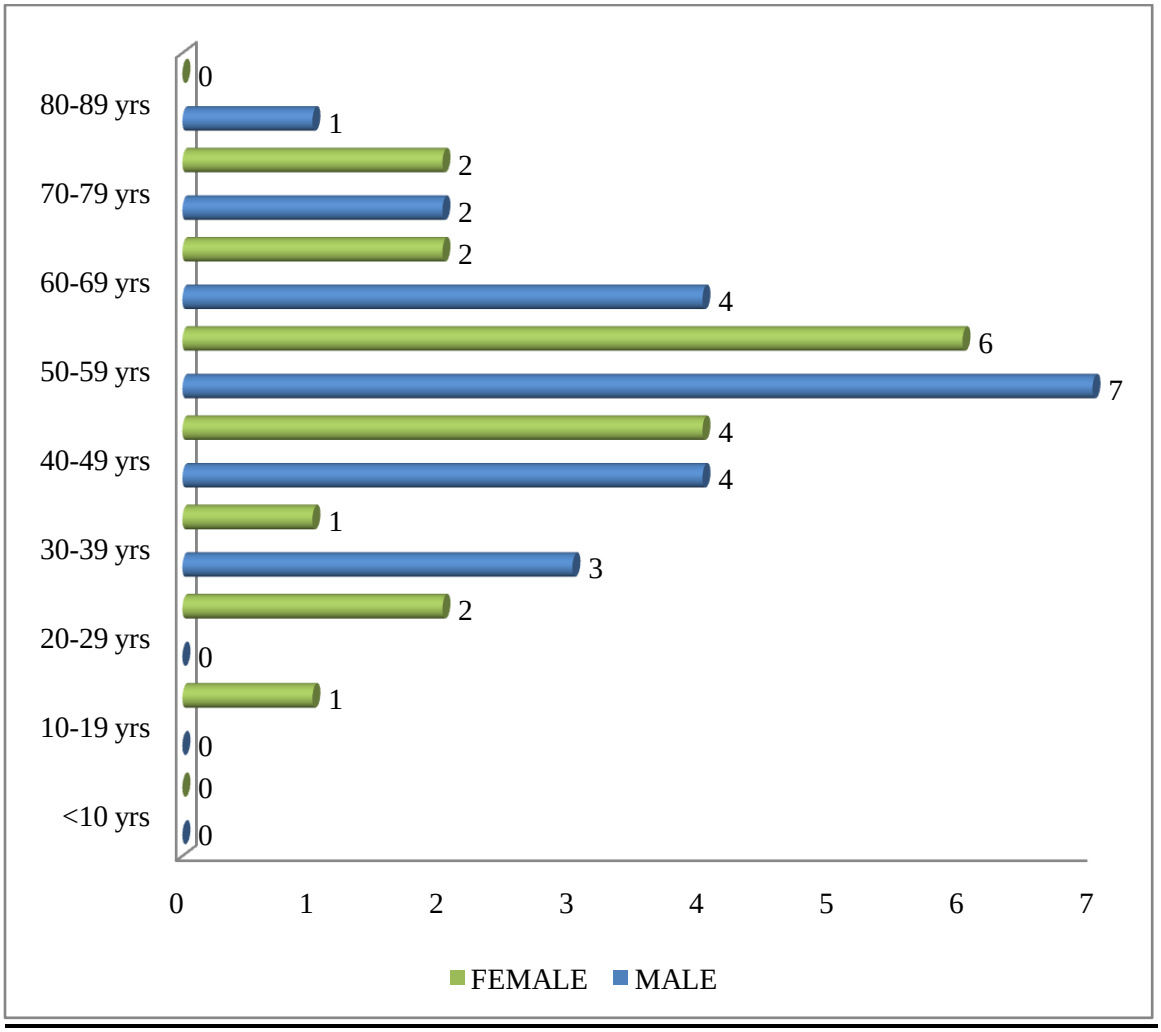


TABLE 17: SEX-WISE INCIDENCE OF INDIVIDUAL SOFT TISSUE TUMOURS

TUMOUR TYPE	MALE		FEMALE	
	NUMBER	PERCENTAGE	NUMBER	PERCENTAGE
ADIPOCYTIC TUMOUR	8	15.38%	3	6.25%
FIBRO/MYOFIBROBLASTIC TUMOUR	7	13.46%	8	16.67%
FIBROHISTIOCYTIC TUMOUR	2	3.85%	3	6.25%
VASCULAR TUMOUR	3	5.77%	3	6.25%
PERIVASCULAR TUMOUR	1	1.92%	0	0%
NERVE SHEATH TUMOUR	15	29%	21	44%
SMOOTH MUSCLE TUMOUR	3	5.77%	1	2.08%
SKELETAL MUSCLE TUMOUR	0	0%	1	2.08%
UNDIFFERENTIATED TUMOUR	7	13.46%	4	8.33%
TUMOUR OF UNCERTAIN DIFFERENTIATION	6	11.53%	4	8.33%
TOTAL	52	100%	48	100%

In the present study, the sex wise incidence of soft tissue tumours revealed that the most common soft tissue tumours in both males and females were nerve sheath tumours constituting about 28.84% and 43.75% respectively. The second most common soft tissue tumour was adipocytic tumours in males (15.38%) and fibroblastic tumours in females (16.67%) (Table 17 and charts 13, 14)

CHART 13- INCIDENCE OF SOFT TISSUE TUMOURS IN MALES

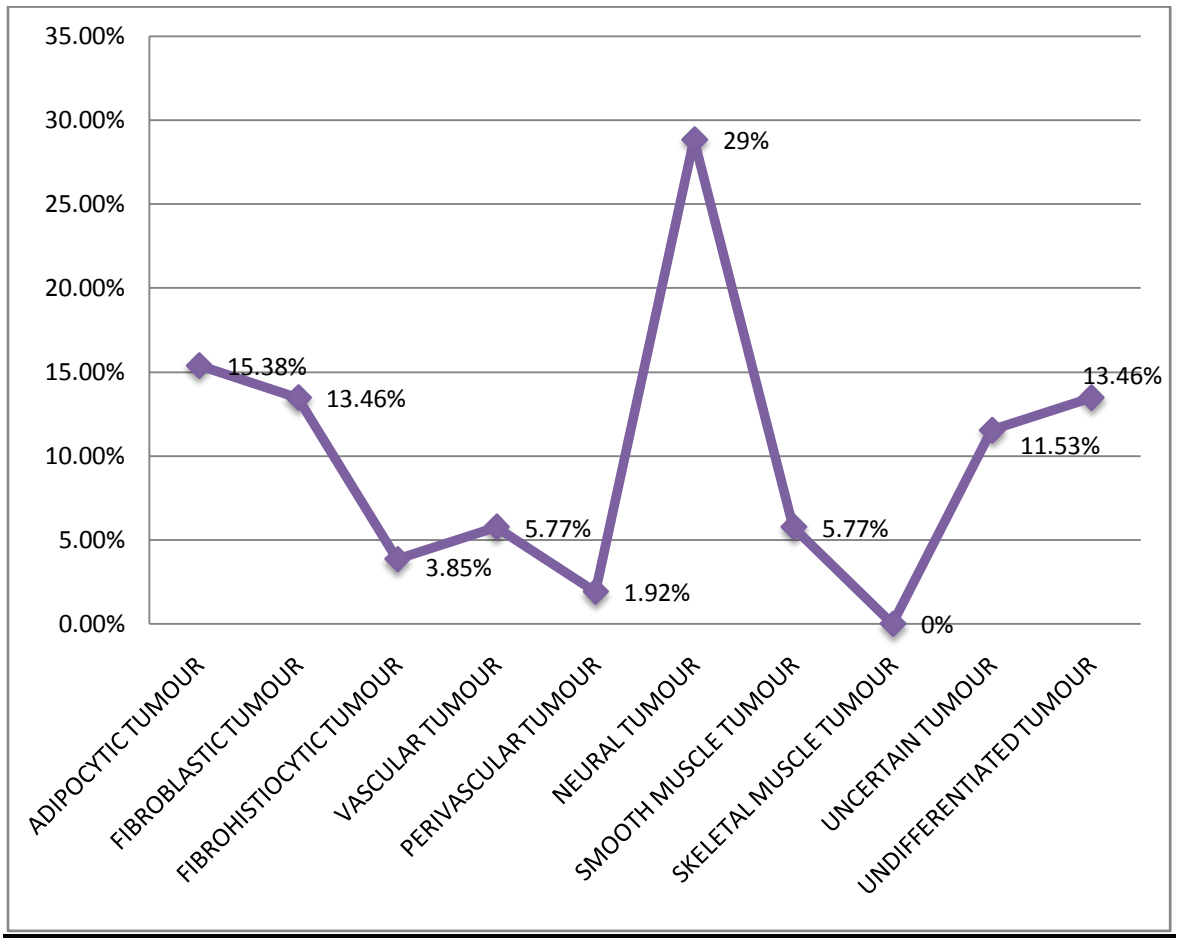


CHART 14- INCIDENCE OF SOFT TISSUE TUMOURS IN FEMALES

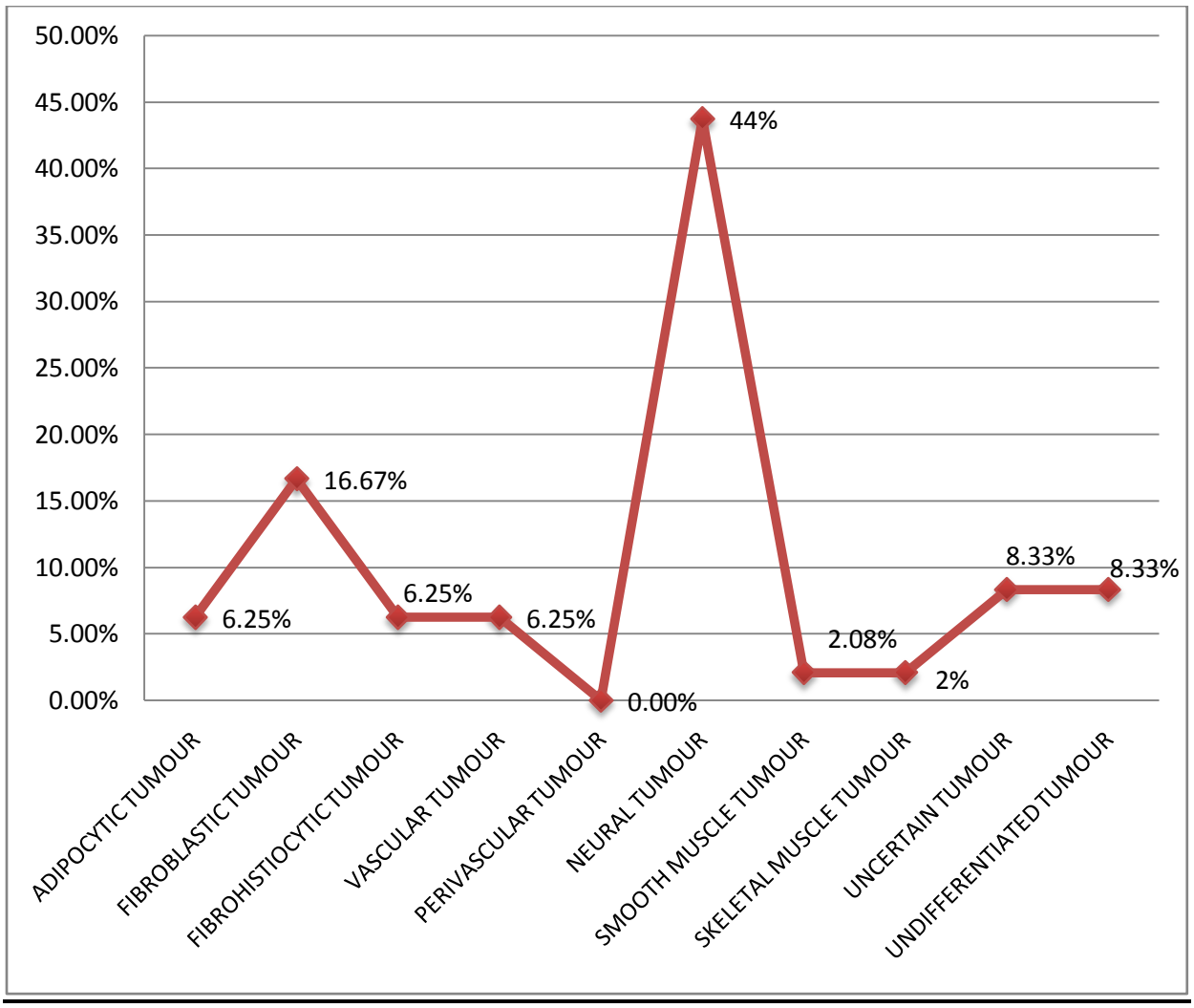


TABLE 18- FNCLCC GRADING OF SOFT TISSUE SARCOMAS

DIAGNOSIS	GRADE 1	GRADE 2	GRADE 3	TOTAL
WELL DIFFERENTIATED LIPOSARCOMA	3	0	0	3
MYXOID LIPOSARCOMA	3	0	1	4
DEDIFFERENTIATED LIPOSARCOMA	0	0	3	3
FIBROSARCOMA	1	4	1	6
INFANTILE FIBROSARCOMA	0	1	0	1
MPNST	1	0	2	3
SYNOVIAL SARCOMA	0	6	1	7
EXTRASKELETAL CHONDROSARCOMA	0	1	0	1
ALVEOLAR SOFT PART SARCOMA	0	1	0	1
ALVEOLAR RHABDOMYOSARCOMA	0	1	0	1
LEIOMYOSARCOMA	1	0	1	2
UNDIFFERENTIATED PLEOMORPHIC SARCOMA	0	2	9	11
TOTAL	9	16	18	43
PERCENTAGE	21	37	42	100%

In the present study, 42% of soft tissue sarcomas were 'grade 3' according to FNCLCC grading system followed by 37% of 'grade 2' sarcomas and 21% of 'grade 1' sarcomas. Out of 18 'grade 3' sarcomas, 9 cases were Undifferentiated pleomorphic sarcomas constituting about 50% of cases followed by 3 cases of dedifferentiated liposarcomas (16.66%). Most frequent among 'grade 2' sarcomas were Synovial sarcoma (37.5%) and fibrosarcoma (25%). Most frequent among 'grade 1' sarcomas were well differentiated and myxoid liposarcomas each accounting for about 33.33%. (Table 18 and charts 13 and 14)

CHART 15- GRADING OF SOFT TISSUE SARCOMAS

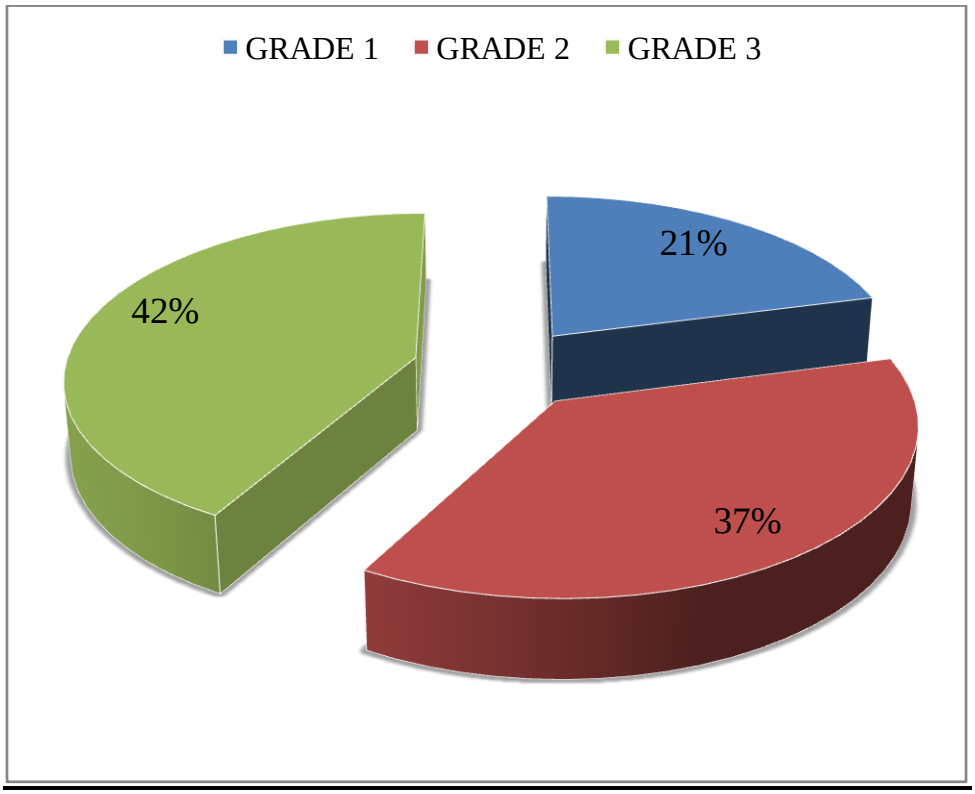


CHART 16- DISTRIBUTION OF SOFT TISSUE SARCOMAS

ACCORDING TO FNCLCC GRADE

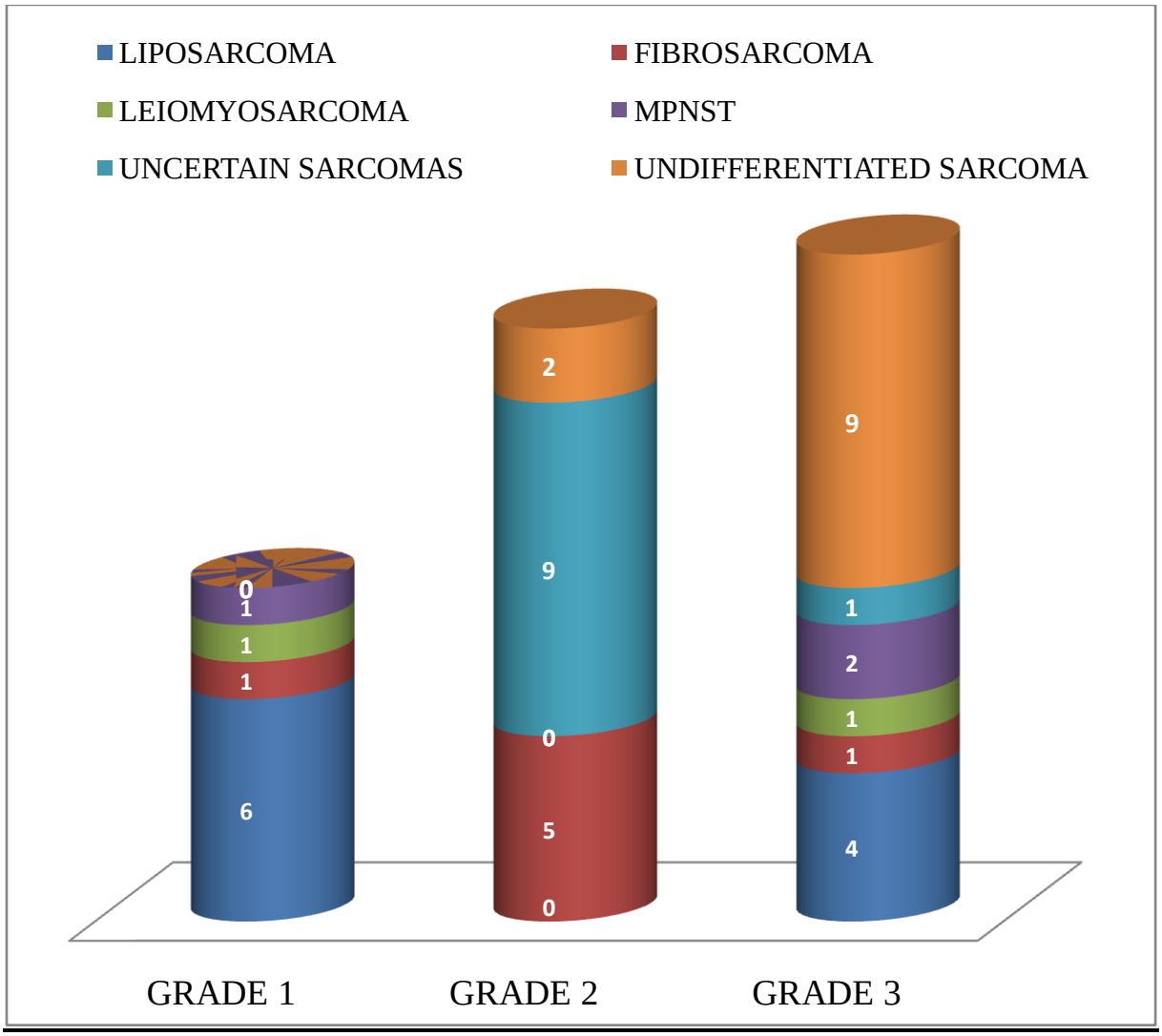


TABLE 19- CORRELATION BETWEEN FNCLCC GRADING AND KI-67 INDEX IN SELECTED CASES

S. NO.	DIAGNOSIS	FNCLCC GRADE	KI 67 SCORE	KI67 INDEX
1	WELL DIFFERENTIATED LIPOSARCOMA	1	1	LOW
2	DEDIFFERENTIATED LIPOSARCOMA	3	3	HIGH
3	FIBROSARCOMA	2	2	HIGH
4	INFANTILE FIBROSARCOMA	2	2	HIGH
5	UNDIFFERENTIATED PLEOMORPHIC SARCOMA	3	2	HIGH
6	MALIGNANT PERIPHERAL NERVE SHEATH TUMOUR	3	2	HIGH
7	LEIOMYOSARCOMA	3	3	HIGH
8	ALVEOLAR RHABDOMYOSARCOMA	2	1	LOW
9	SYNOVIAL SARCOMA	2	1	LOW
10	ALVEOLAR SOFT PART SARCOMA	2	1	LOW

- Spearman's Rho correlation (R) = 0.77 with p value of 0.005
- Pearman's correlation coefficient (R) =0.75 with p value of 0.007

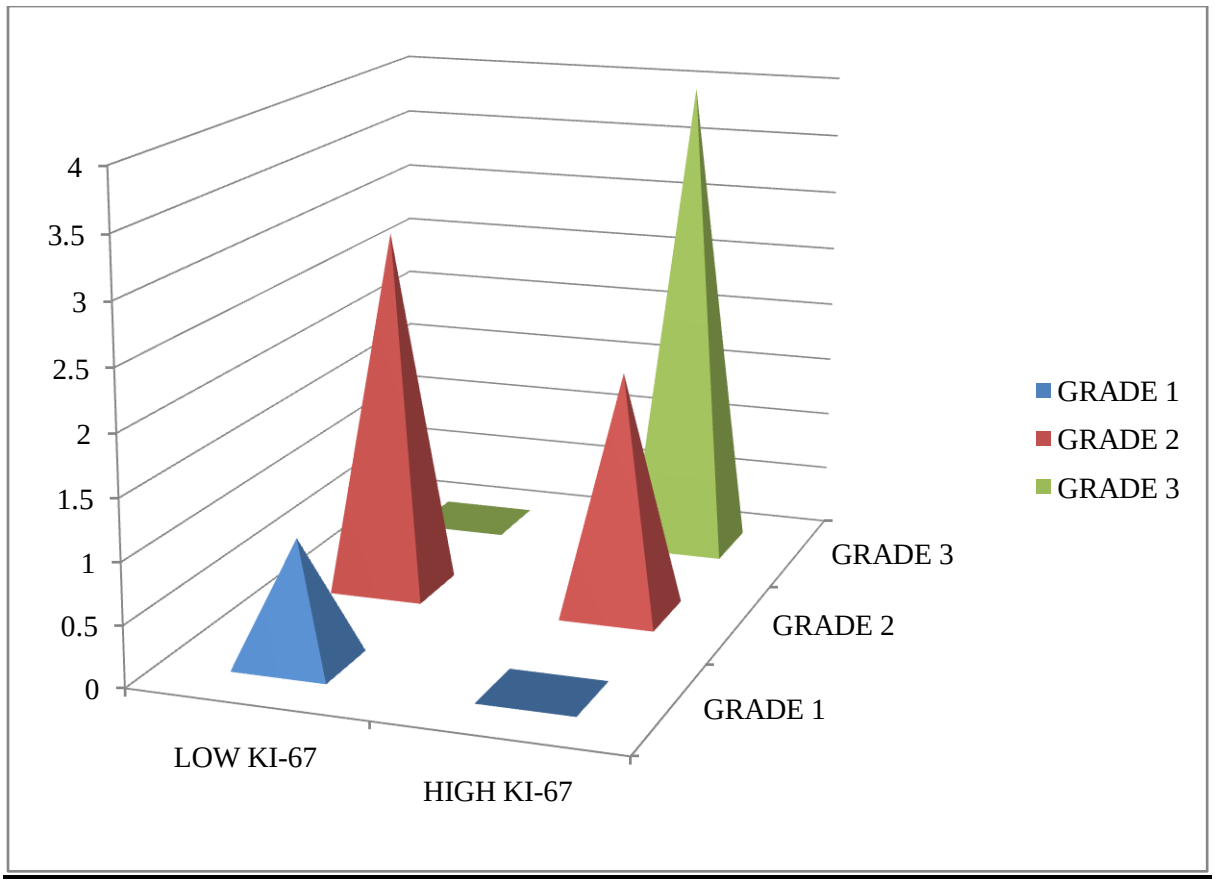
TABLE 20- CORRELATION OF KI-67 INDEX AND FNCLCC GRADE

KI 67 PROLIFERATIVE INDEX	GRADE 1	GRADE 2	GRADE 3	TOTAL
HIGH	0	2	4	6
LOW	1	3	0	4

In the present study, Grade 1 sarcoma (n=1) had a low Ki-67 index with score of 1 (1-25%). Among Grade 2 sarcomas (n=5), two cases had high Ki-67 index with score of 3 (more than 50%) and three had low Ki-67 index with score of 2 (26-50%). All the four grade 3 sarcomas had high Ki-67 index. Spearman's rho and Pearson's correlation coefficients were calculated and the p value was less than 0.05.(Tables 19, 20 and chart 17).

The relationship between tumour histologic grade and Ki-67 index is statistically significant. Hence Ki-67 index has a positive correlation with histological grade in the present study.

CHART 17- CORRELATION OF FNCLCC GRAGE AND KI-67 INDEX



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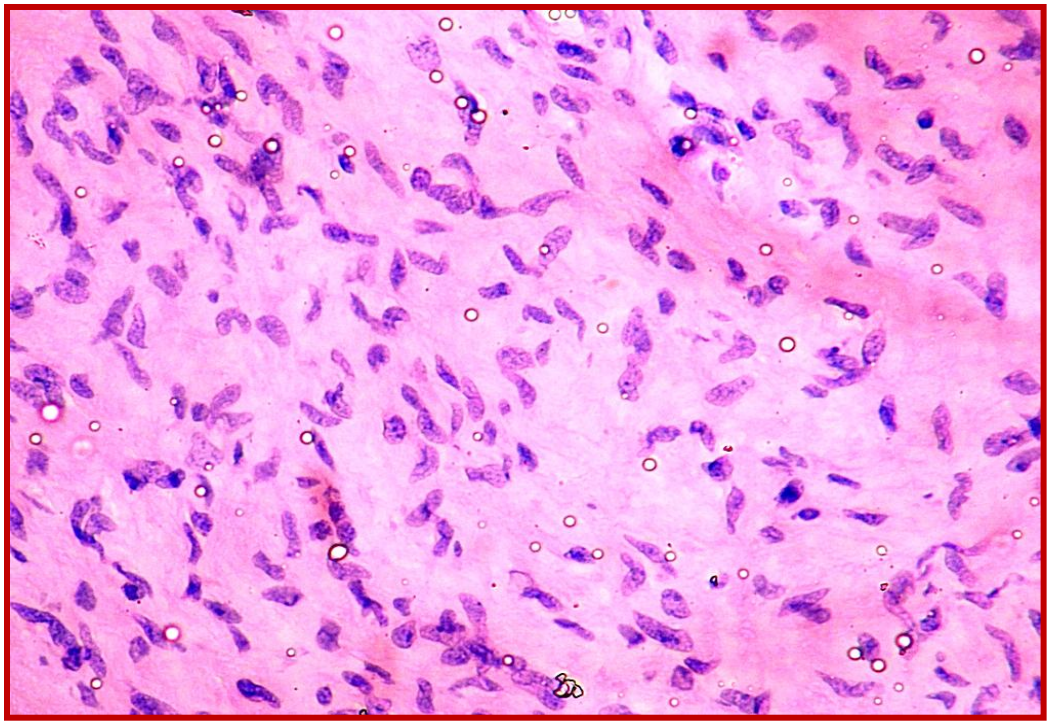

Figure 1- Neurofibroma - spindle shaped tumour cells with wavy buckled nuclei (H&E 400x) Case 934/15

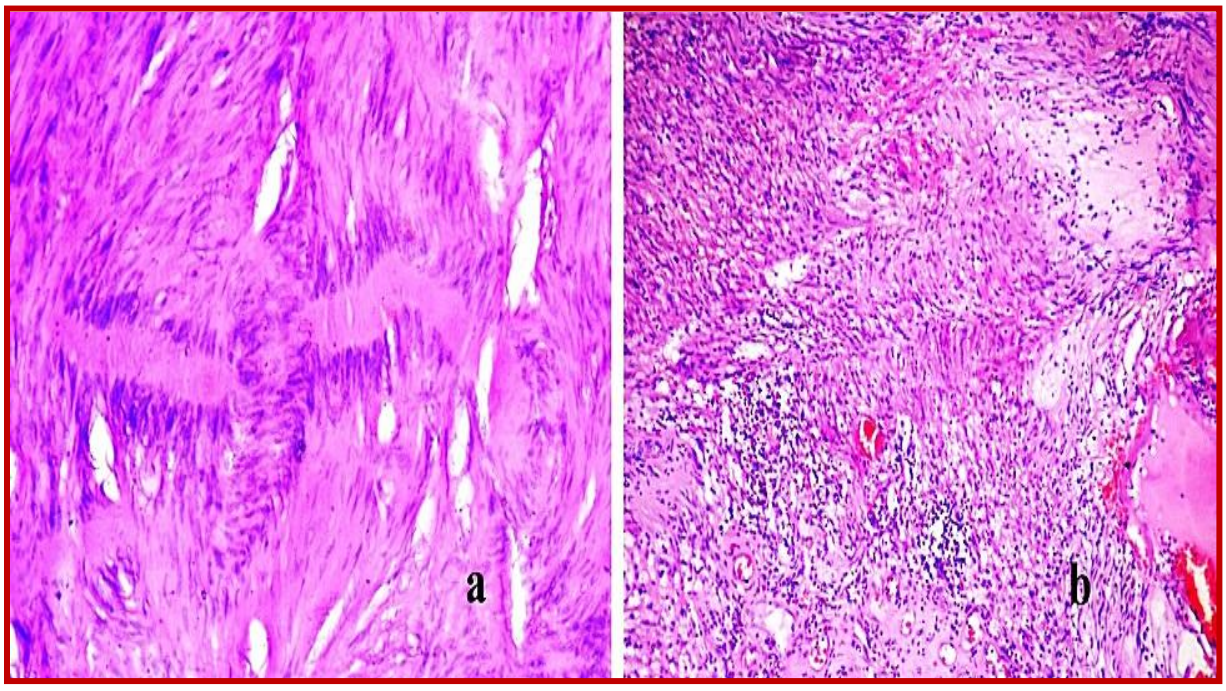

Figure 2- Schwannoma - a) Antoni A area with Verrocay bodies (H&E 400x) Case 534/16 b) Ancient schwannoma with degenerative changes (H&E 100x) Case 4146/14

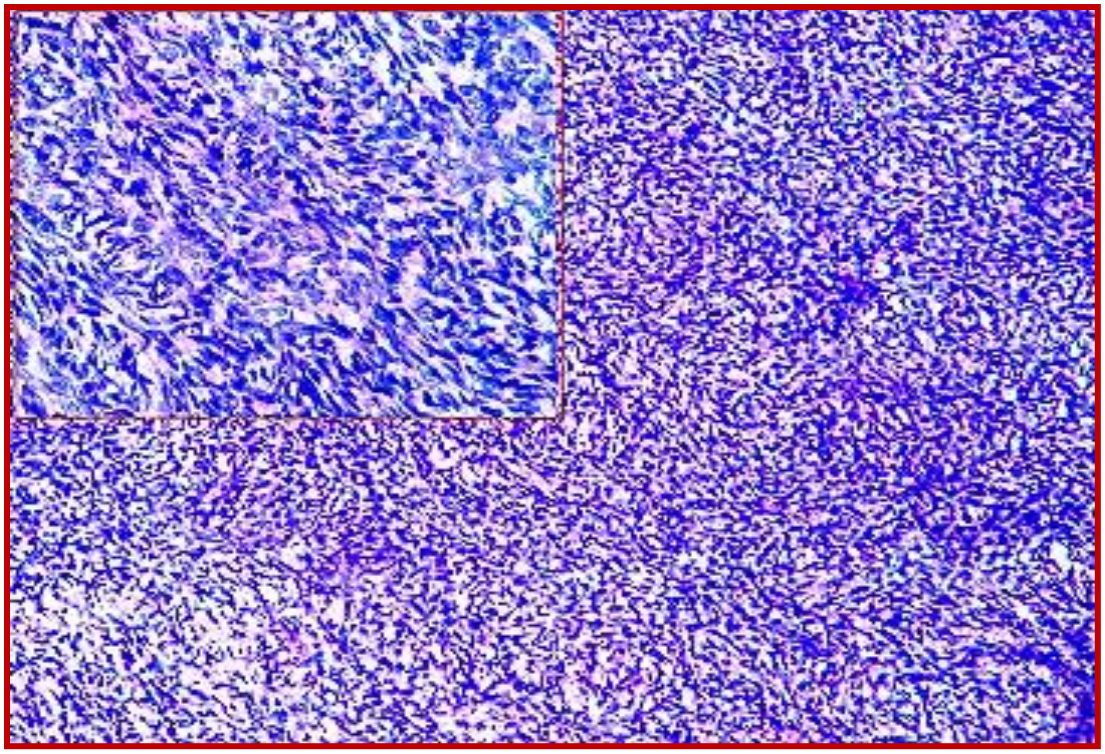

Figure 3 - BFH- storiform pattern of tumour cells with histiocytes (H&E 100x) Case 2326/16. Inset shows spindle shaped cells with plump nuclei (H&E 400x)

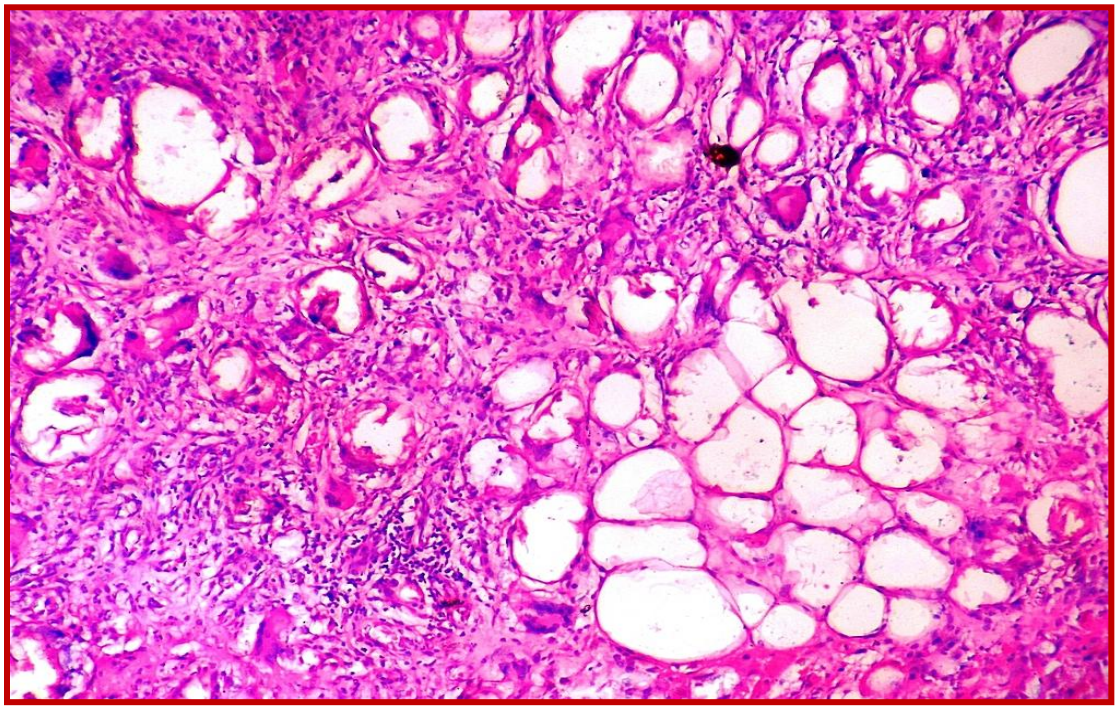

Figure 4- Pleomorphic lipoma- mature adipocytes with stromal atypical cells and floret giant cells (H&E 400x) Case 60/16

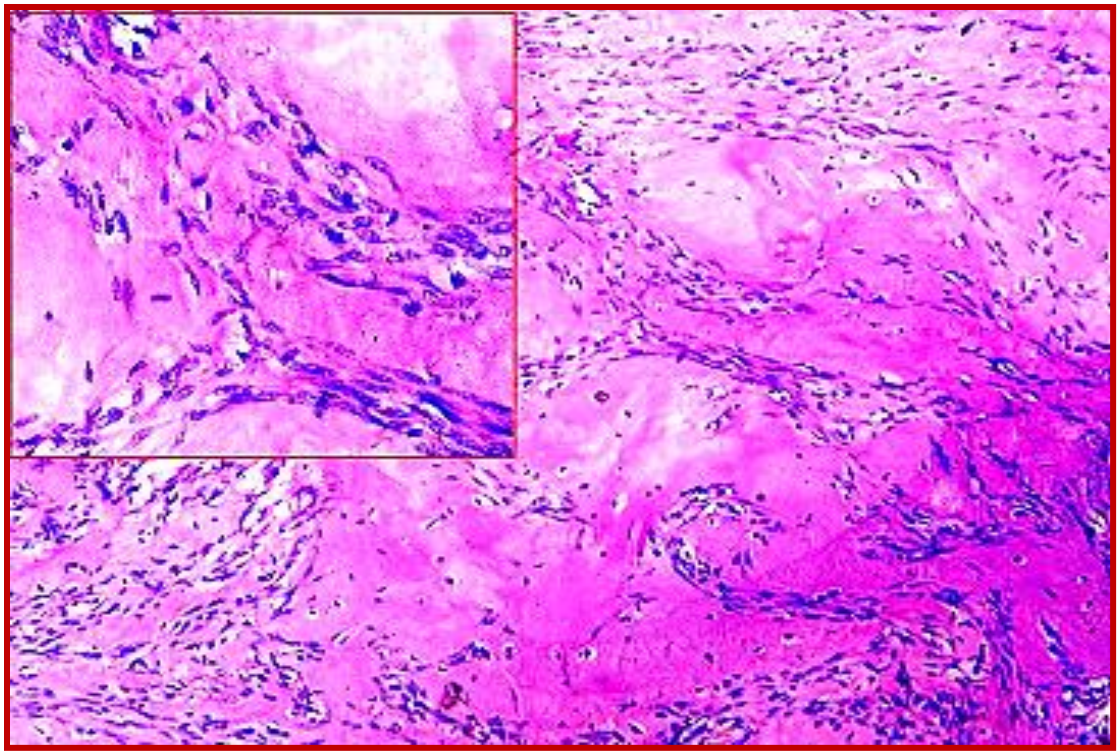

Figure 5 - Juvenile hyaline fibromatosis - fibroblasts are embedded in a dense hyalinised stroma (H&E 100x) Case 2199/16. Inset shows high power (400x) view of tumour

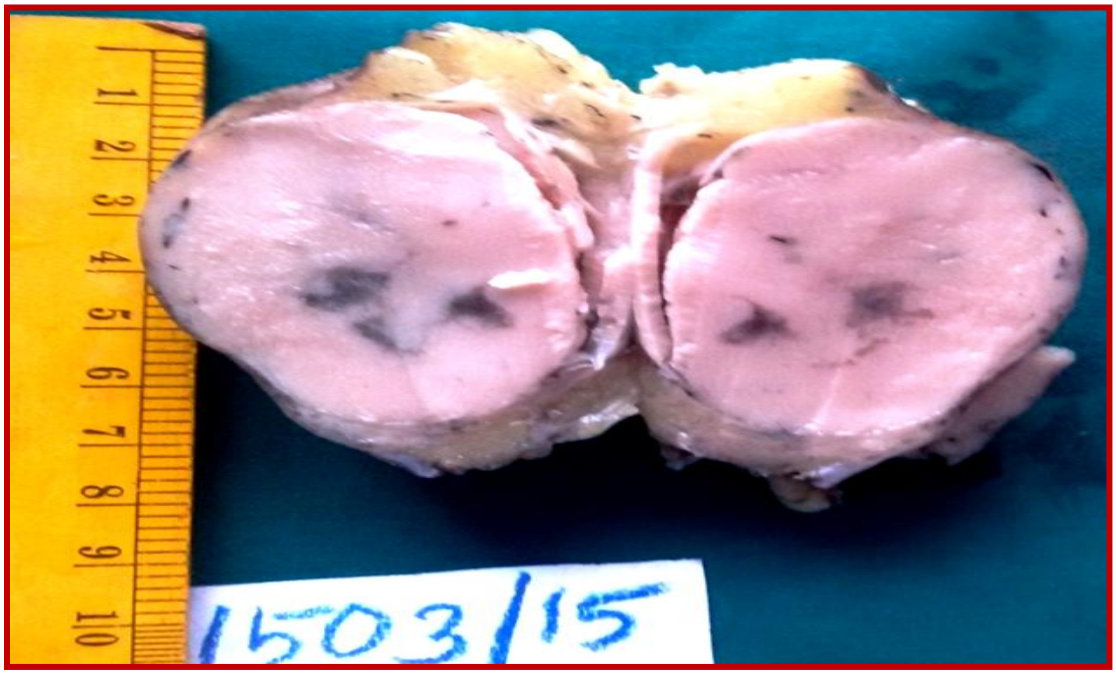

Figure 6 - DFSP macroscopy – tumour with greyish white and greyish brown areas. Case 1503/15

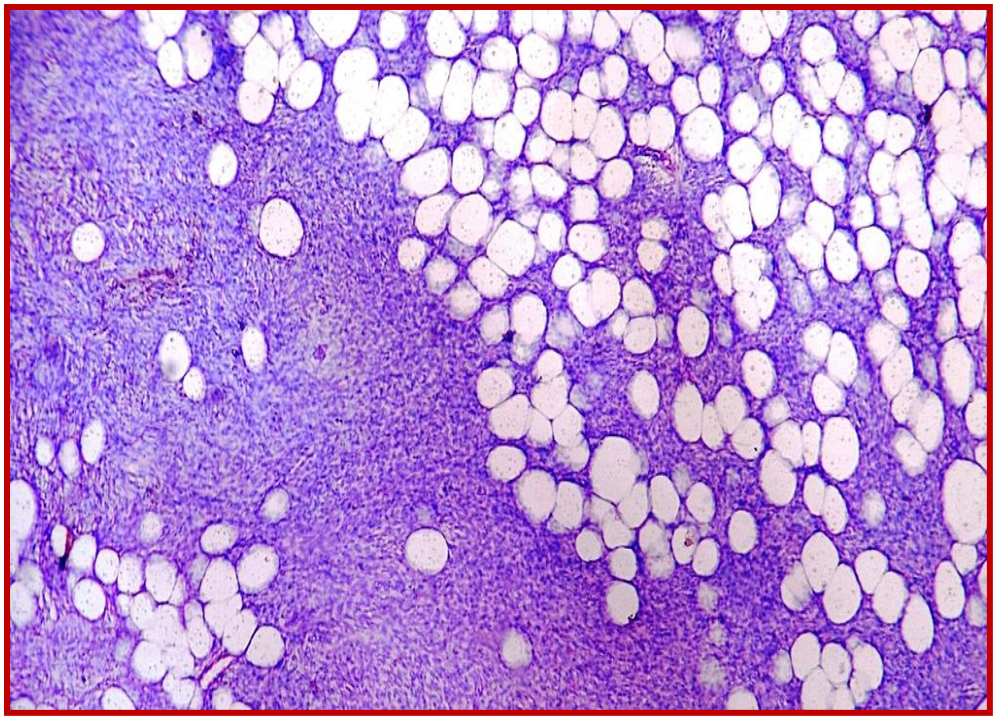

Figure 7 - DFSP - spindle shaped tumour cells arranged in storiform pattern and entrapping subcutaneous fatty tissue (H&E 100x) Case 1503/15

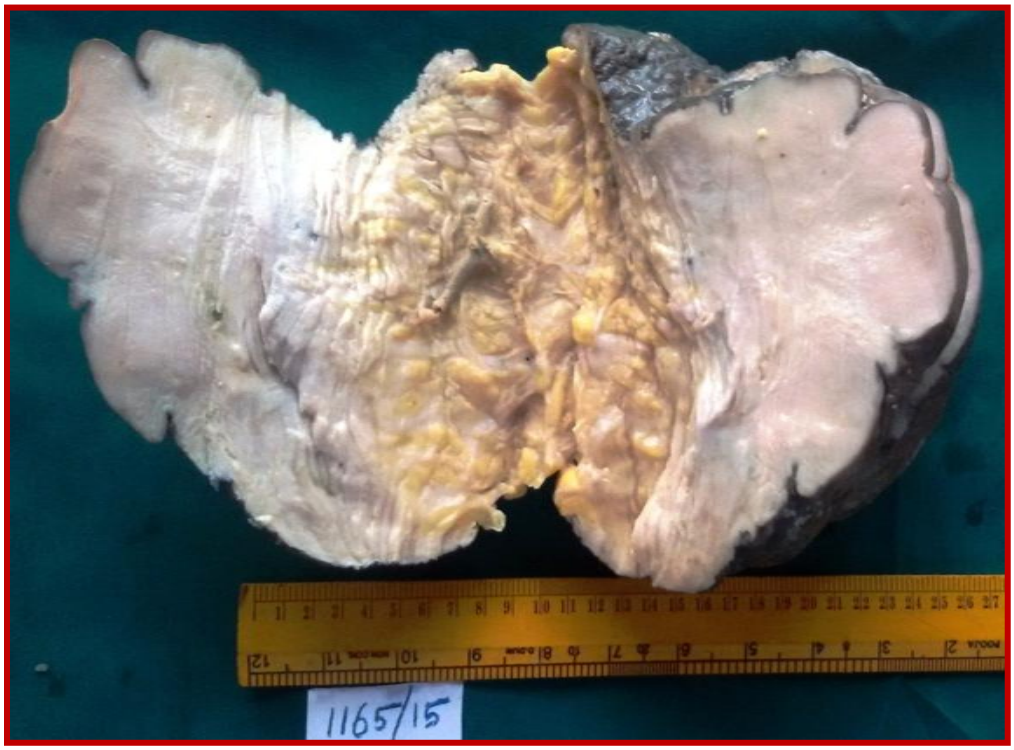

Figure 8 - Well differentiated Liposarcoma macroscopy - tumour with yellowish and greyish white solid areas. Case 1165/15

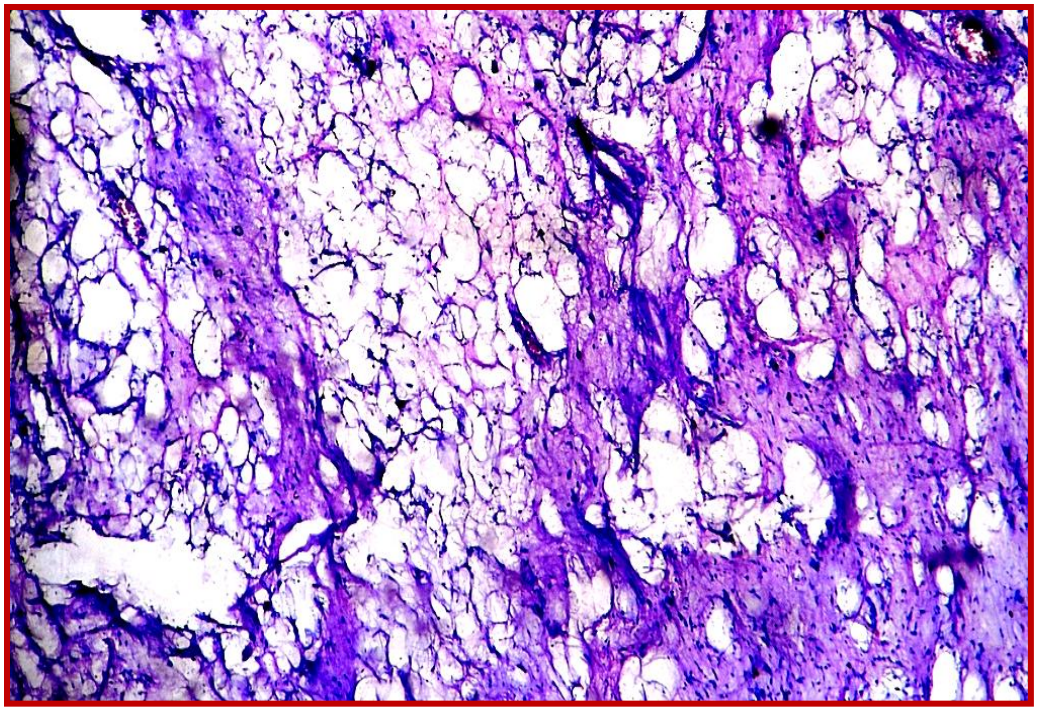

Figure 9 - Well differentiated liposarcoma - mature adipocytes in a stroma showing few atypical cells and lipoblasts (H&E 40x) Case 3595/15.

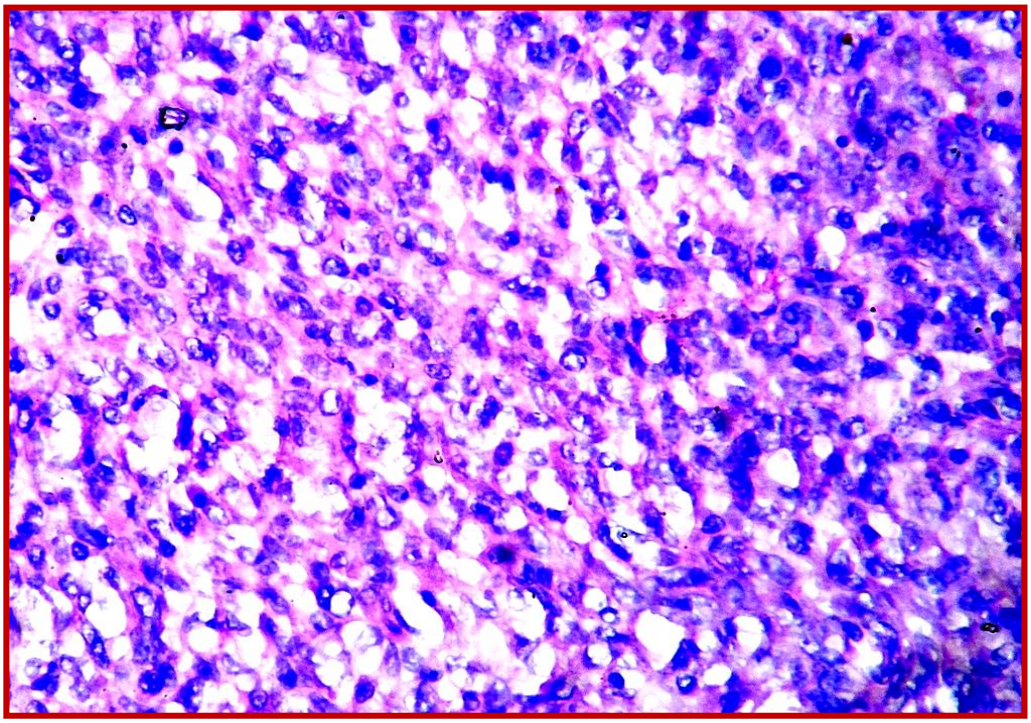

Figure 10- Infantile fibrosarcoma - tumour with round to spindled cells showing nuclear atypia and mitotic activity. (H&E 400x).Case 322/16

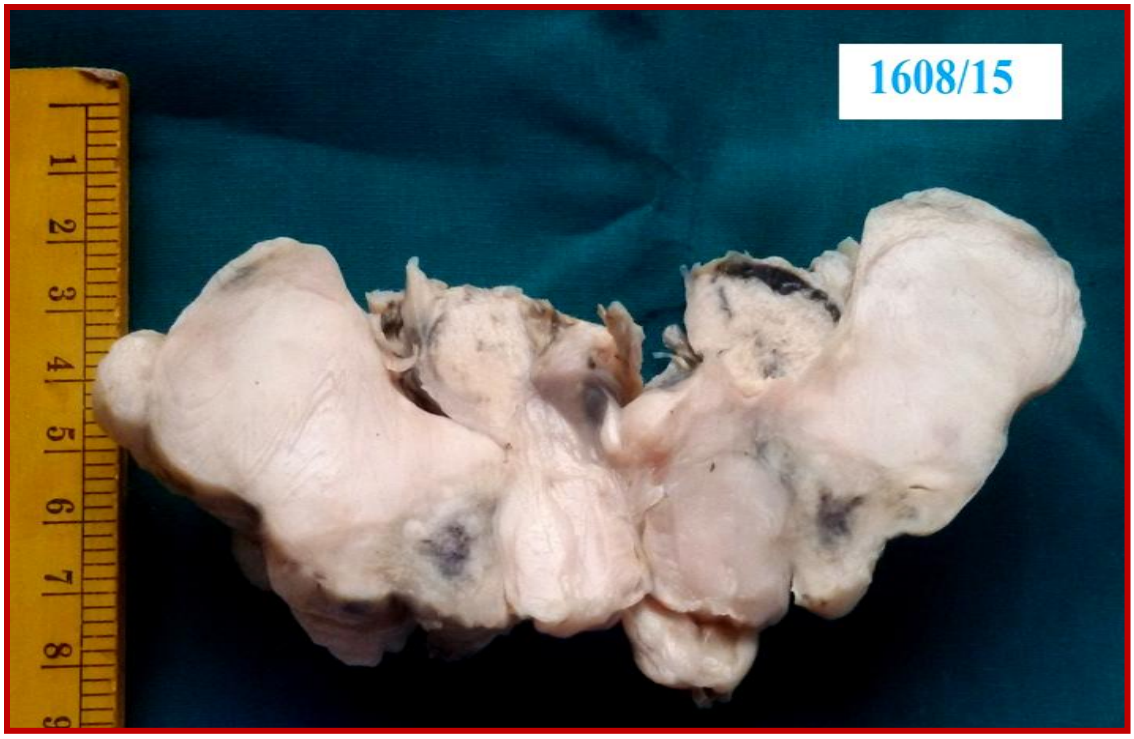

Figure 11 - Undifferentiated pleomorphic sarcoma macroscopy - greyish white firm tumour. Case 1608/15

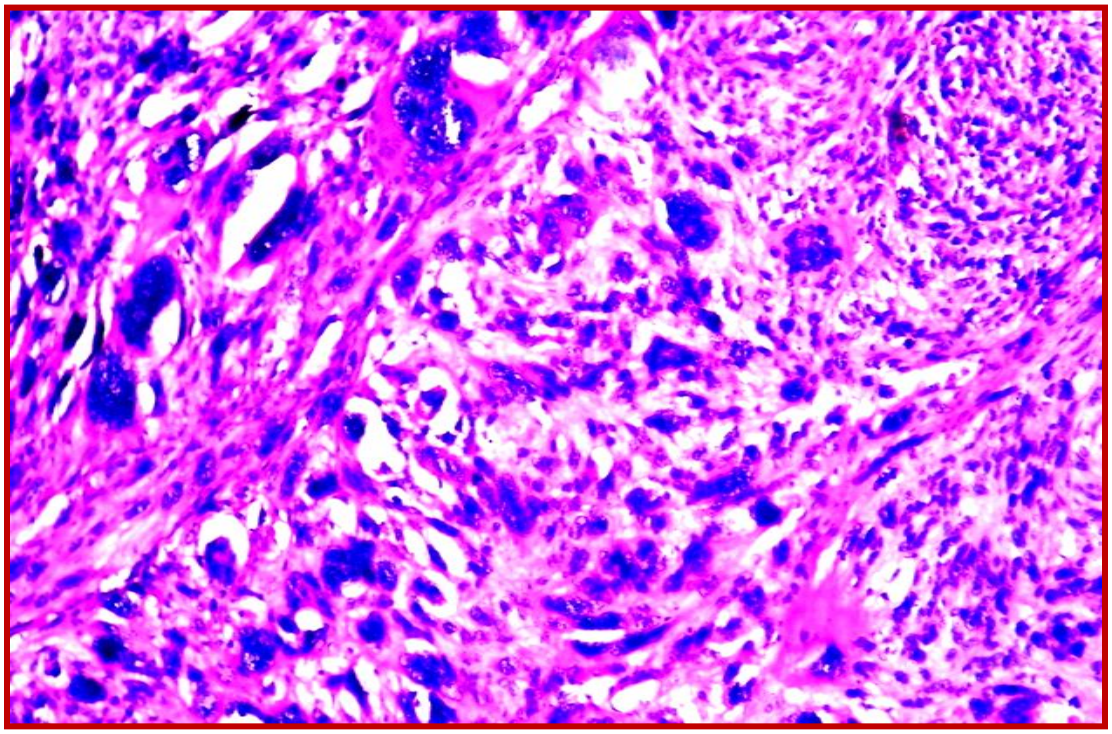

Figure 12- Undifferentiated pleomorphic sarcoma - tumour showing pleomorphic spindled cells with bizarre nuclei (H&E 100x).Case 586/16

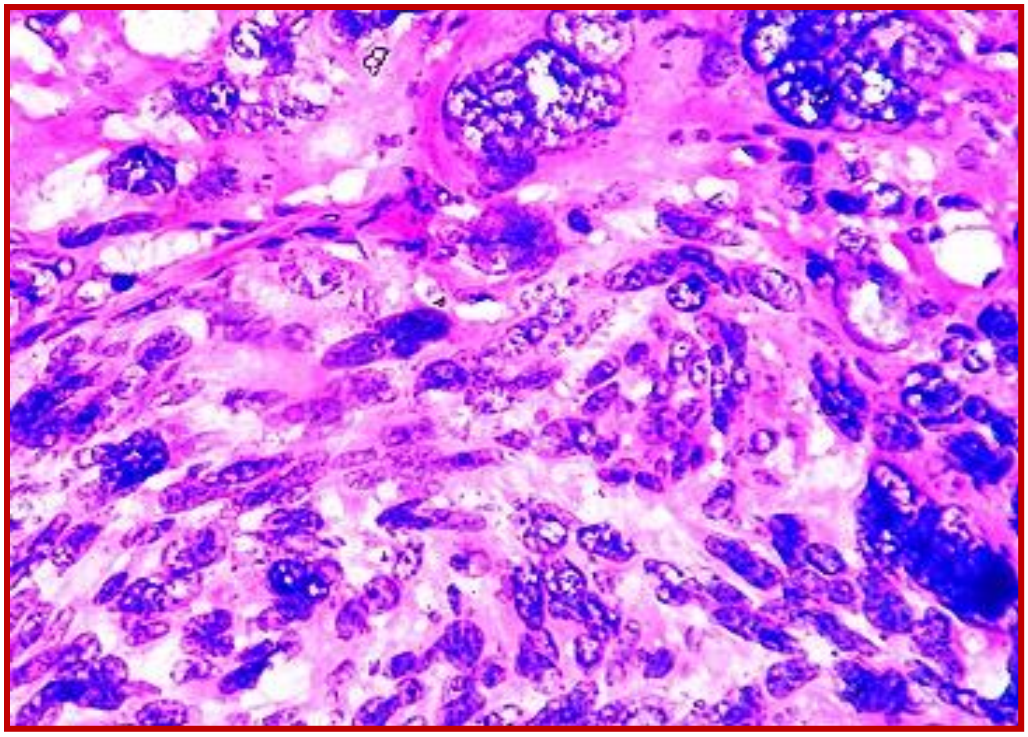

Figure 13 - Undifferentiated pleomorphic sarcoma - tumour cells with high grade nuclear atypia and mitoses seen (H&E 400x) Case 586/16

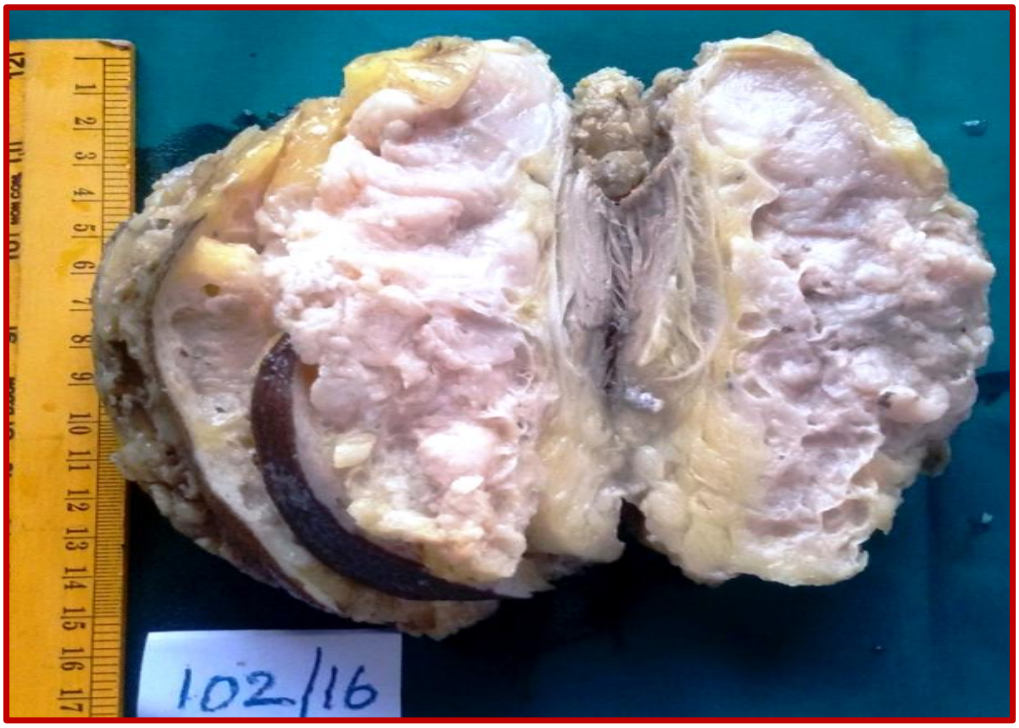

Figure 14 - Myxoid liposarcoma macroscopy- greyish yellow solid tumour with myxoid areas. Case 102/16

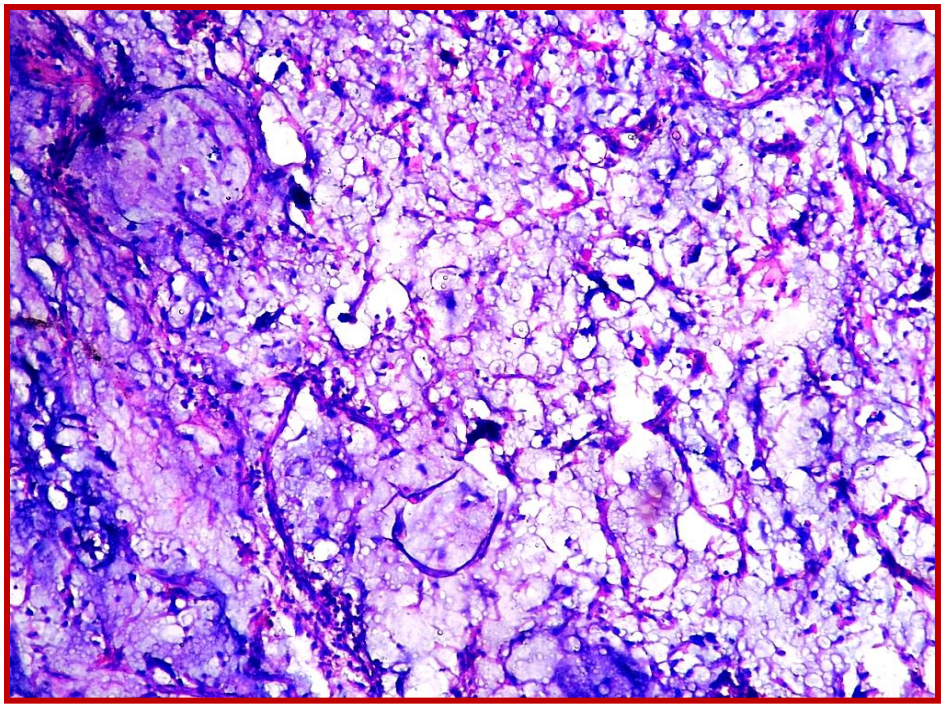

Figure 15- Myxoid liposarcoma- tumour composed of pleomorphic spindled cells, lipoblasts and myxoid areas.(H&E 100x) Case 102/16

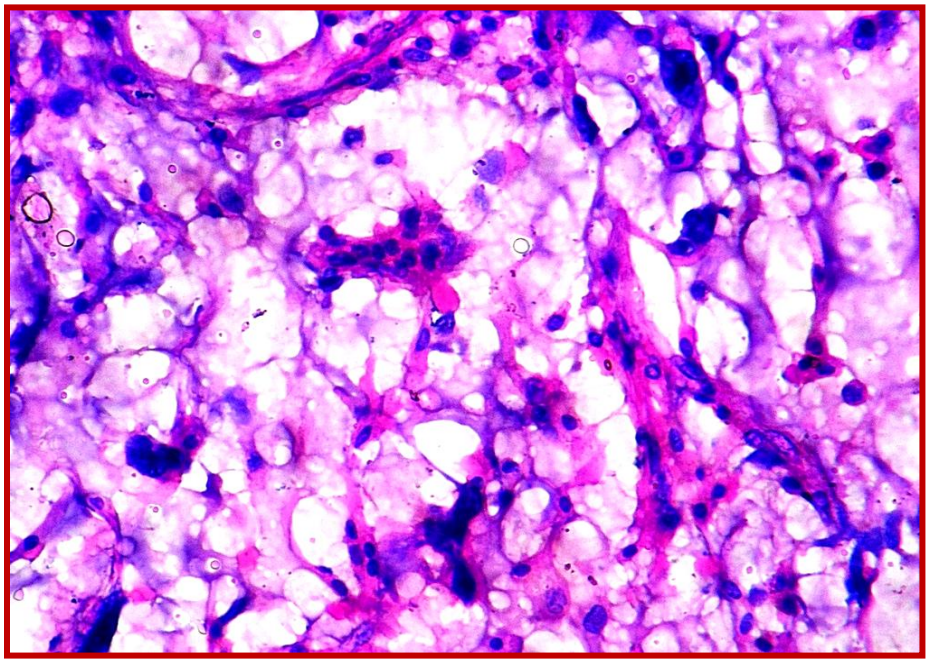

Figure 16 - Myxoid liposarcoma – showing lipoblasts and characteristic chicken-wire blood vessels (H&E – 400x) Case 102/16

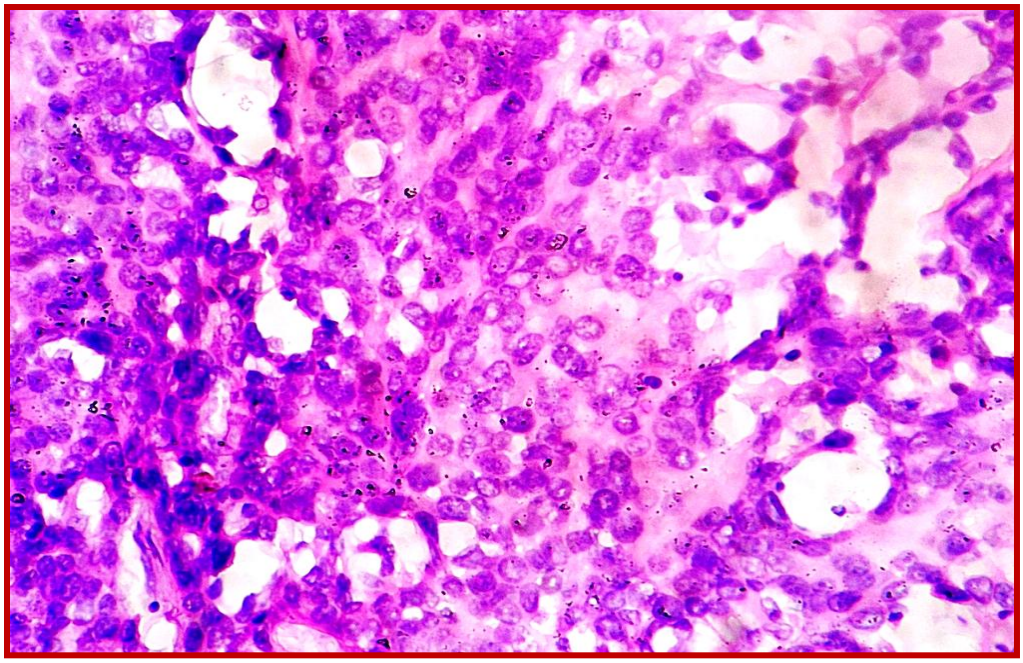

Figure 17 - High grade myxoid liposarcoma- tumour cells are round with hyperchromatic nuclei admixed with lipoblasts. (H&E 400x) Case 1453/16

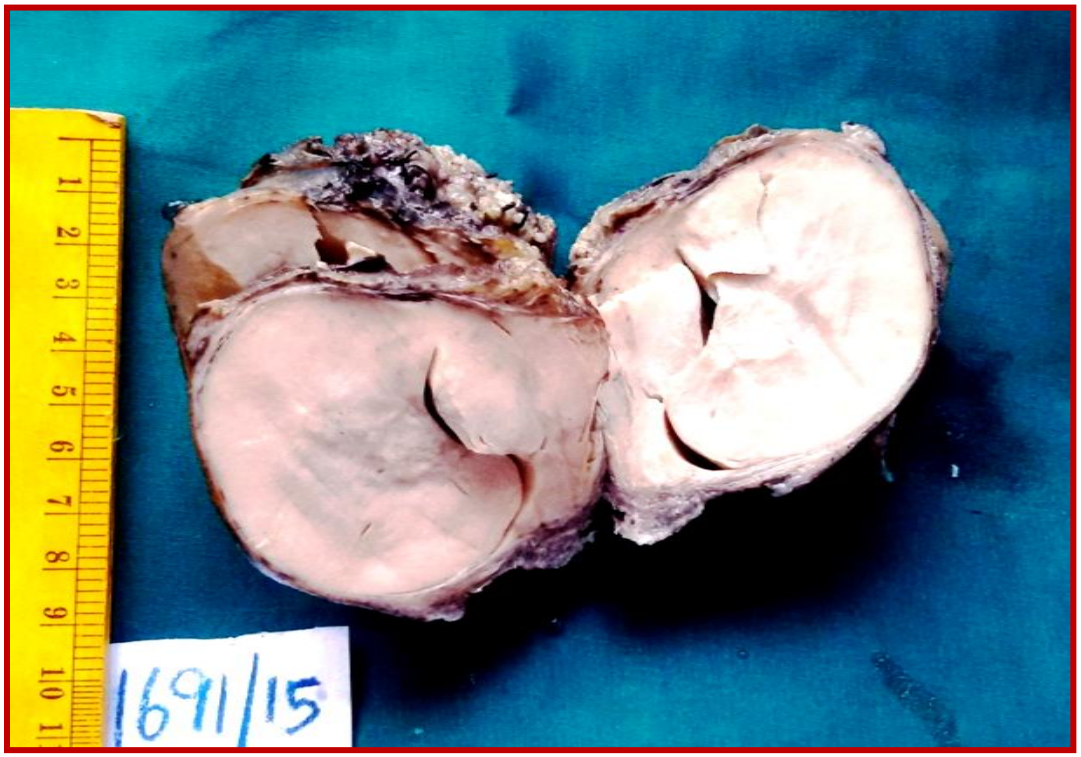

Figure 18 - Dedifferentiated liposarcoma macroscopy - solid greyish white tumour. Case 1691/15

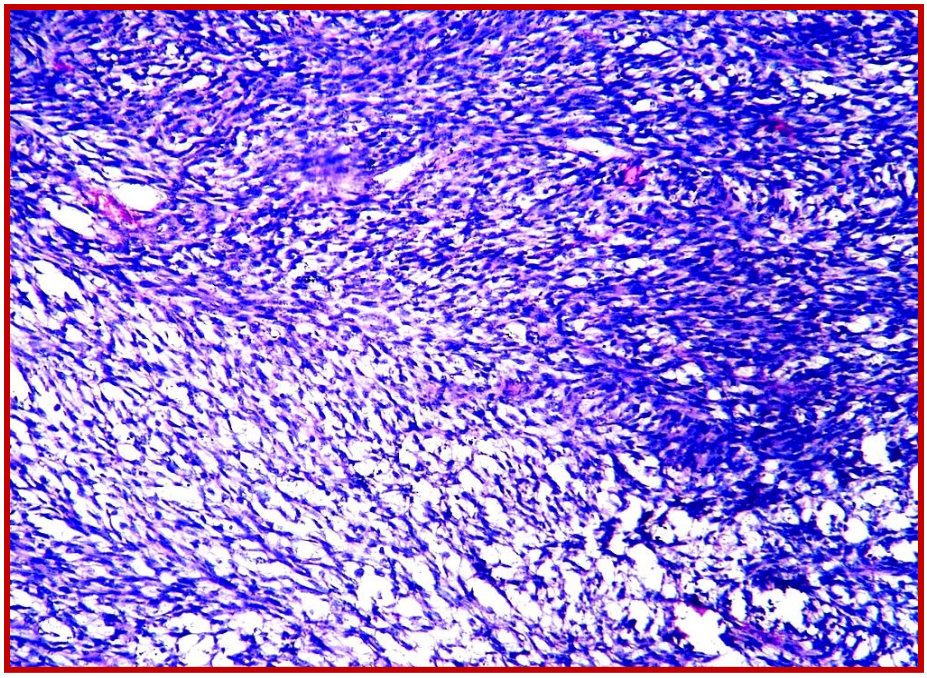

Figure 19a- Dedifferentiated liposarcoma - tumour with lipogenic areas showing abrupt transition to high grade sarcoma.(H&E 100x).Case 108/16

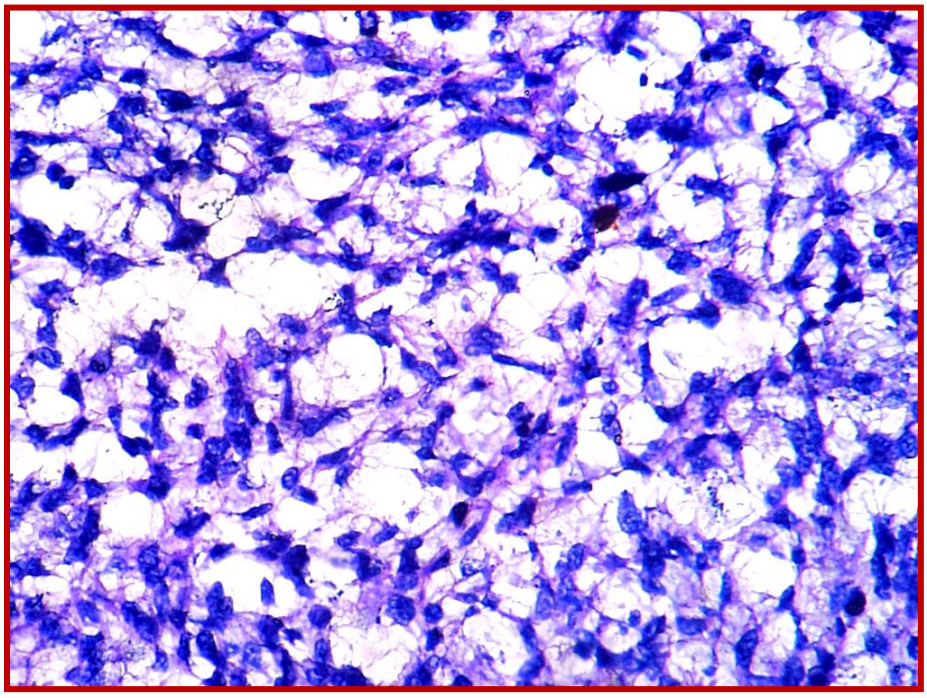

Figure 19b - Dedifferentiated liposarcoma- lipoblasts with indented nuclei and pleomorphic spindled cells. (H&E 400x) Case 108/16

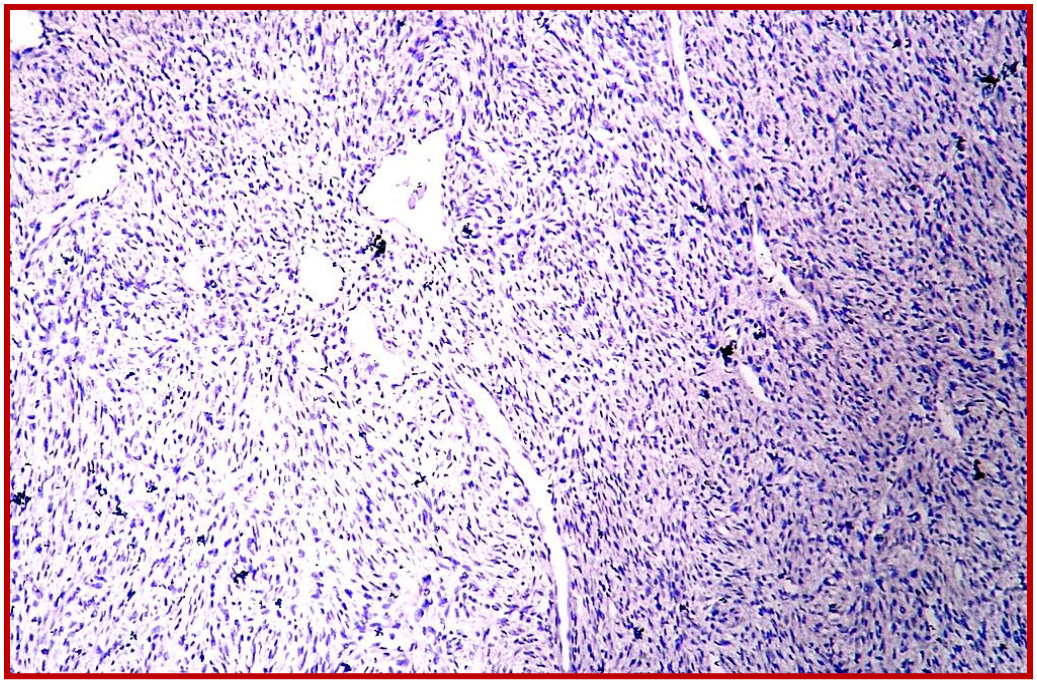

Figure 20 - Synovial sarcoma - biphasic type with spindle shaped cells and round to oval shaped epithelial cells (H&E 40x) Case 1194/15

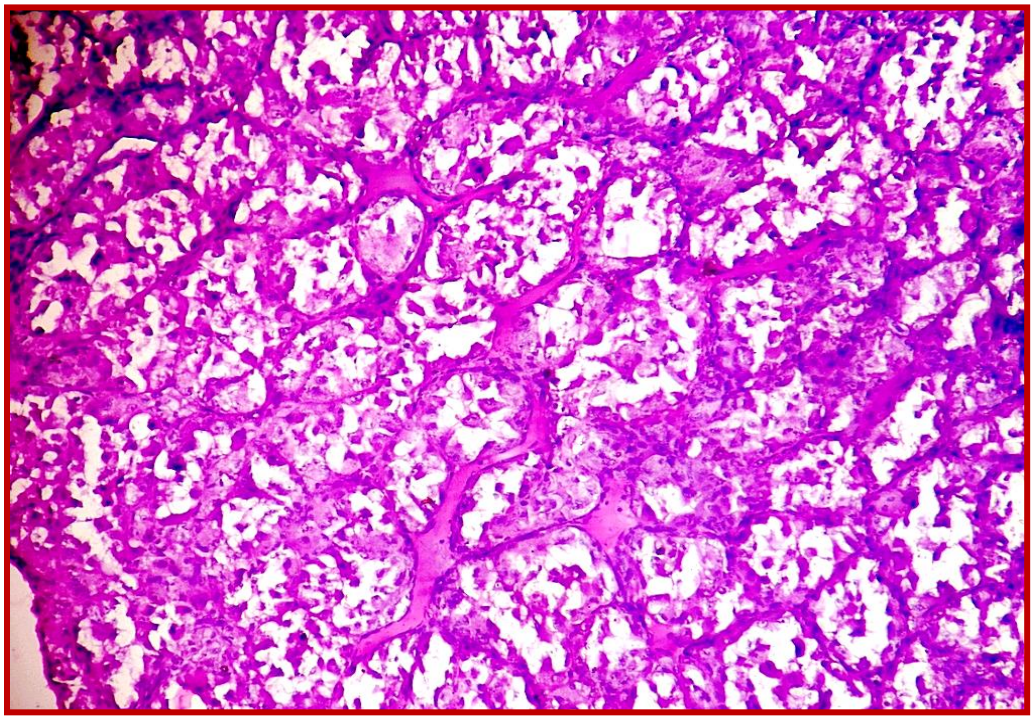

Figure 21 - Alveolar soft part sarcoma - tumour cells have abundant eosinophilic cytoplasm and seen in alveolar pattern (H&E 100x).Case 540/16

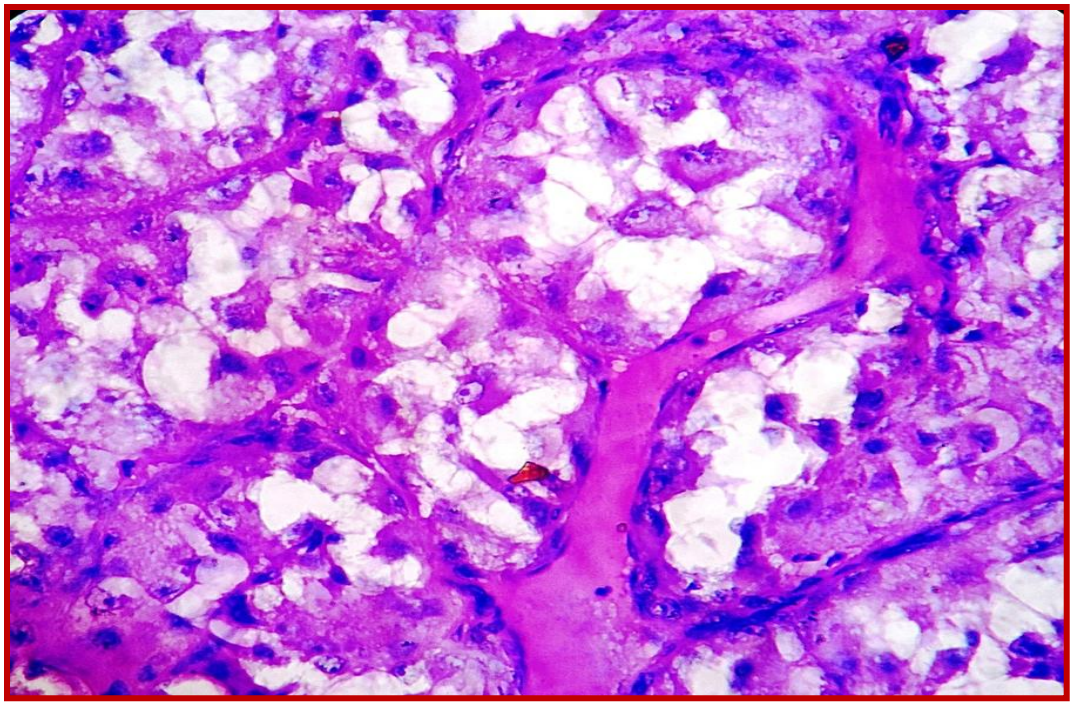

Figure 22- Alveolar soft part sarcoma - tumour cells showing central dyscohesion and separated by thin sinusoidal septa.(H&E 400x) Case 540/16

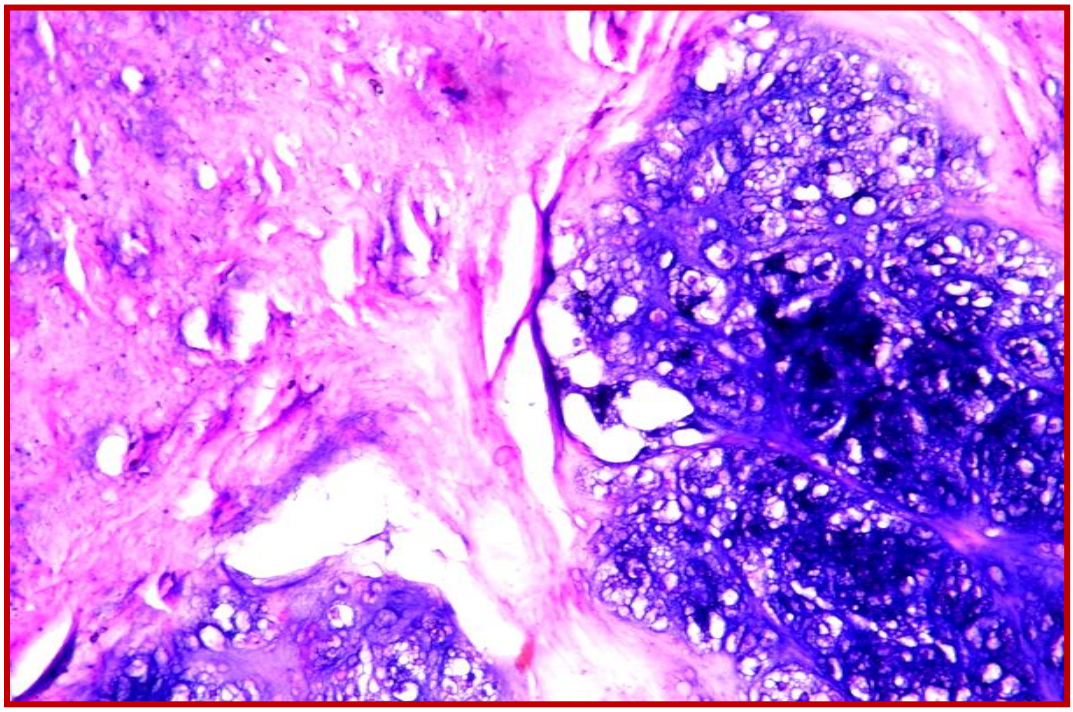

Figure 23 - Extraskeletal myxoid chondrosarcoma- tumour with chondroid and myxoid areas. (H&E 100x).Case 2911/15

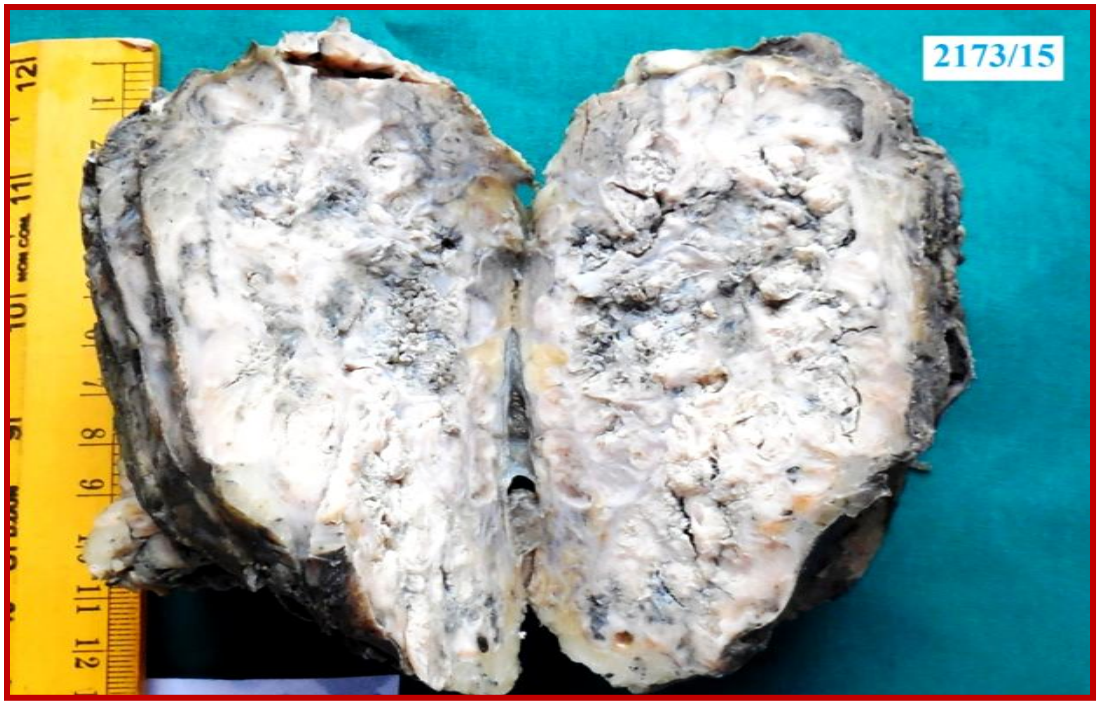

Figure 24 - Fibrosarcoma macroscopy - greyish white solid tumour with areas of necrosis. Case 2173/15

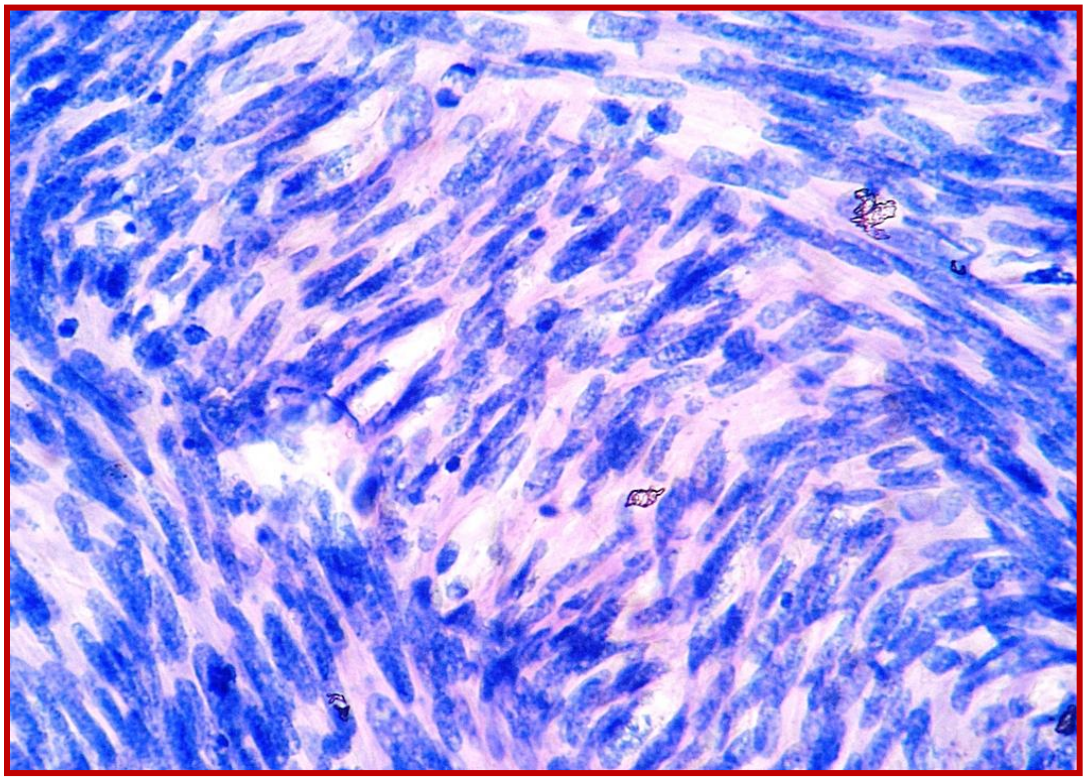

Figure 25 - Fibrosarcoma - spindle shaped tumour cells arranged in Herring bone pattern with increased mitotic activity (H&E 400x) Case 1922/16

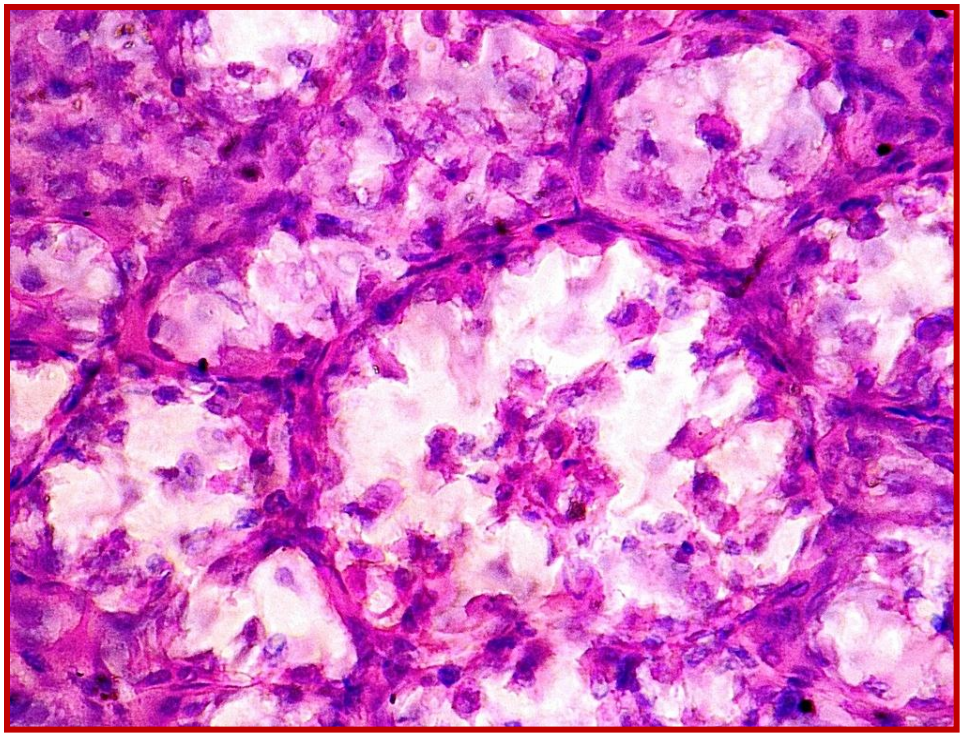

Figure 26- Alveolar rhabdomyosarcoma- tumour cells arranged in alveolar pattern separated by delicate vascular septa (H&E 400x). Case 1368/16

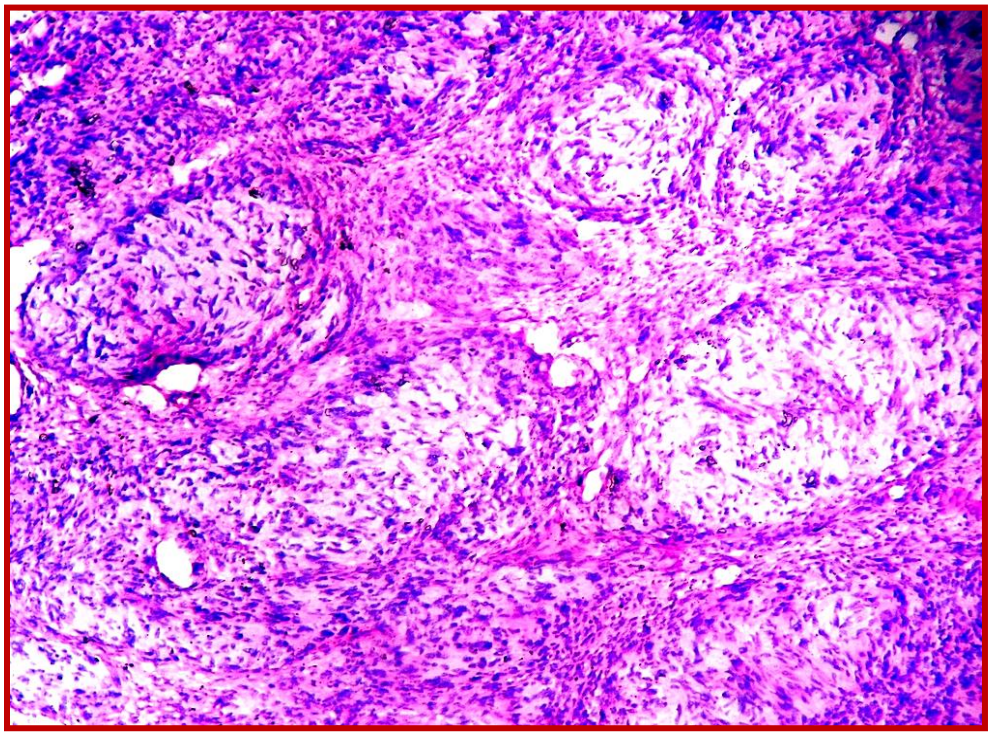

Figure 27a- Well differentiated MPNST - tumour with schwann cell differentiation (H&E 100x).Case 4069/14

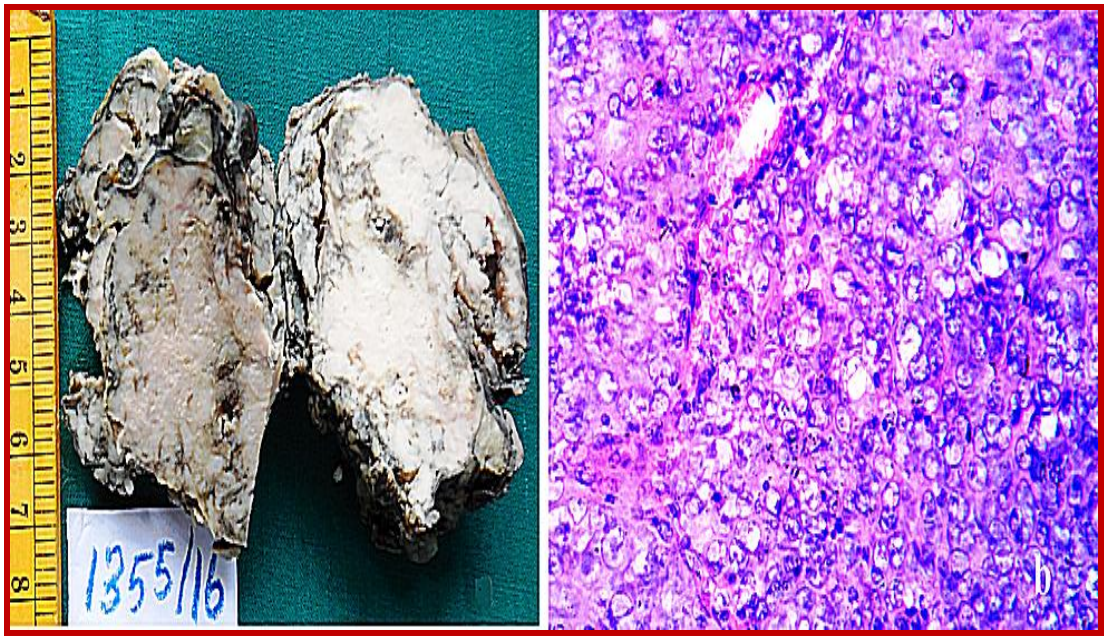

Figure 27b - MPNST- macroscopy and microscopy (H&E 400x) showing epithelioid differentiation. Case 1355/16

Figure 28 - Leiomyosarcoma macroscopy - nodular tumour with greyish white whorled appearance. Case 2694/15

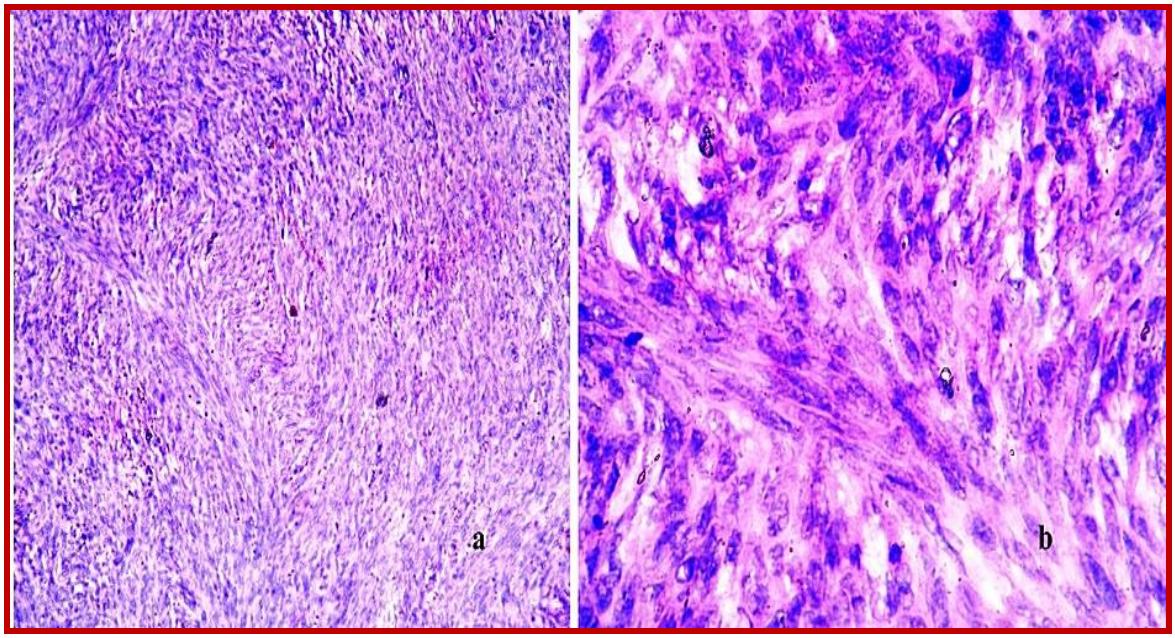

Figure 29 - Leiomyosarcoma a) long fascicular pattern of tumour cells. (H&E 40x) and b) spindle shaped tumour cells with nuclear atypia and mitotic activity(H&E 400x) Case 304/16

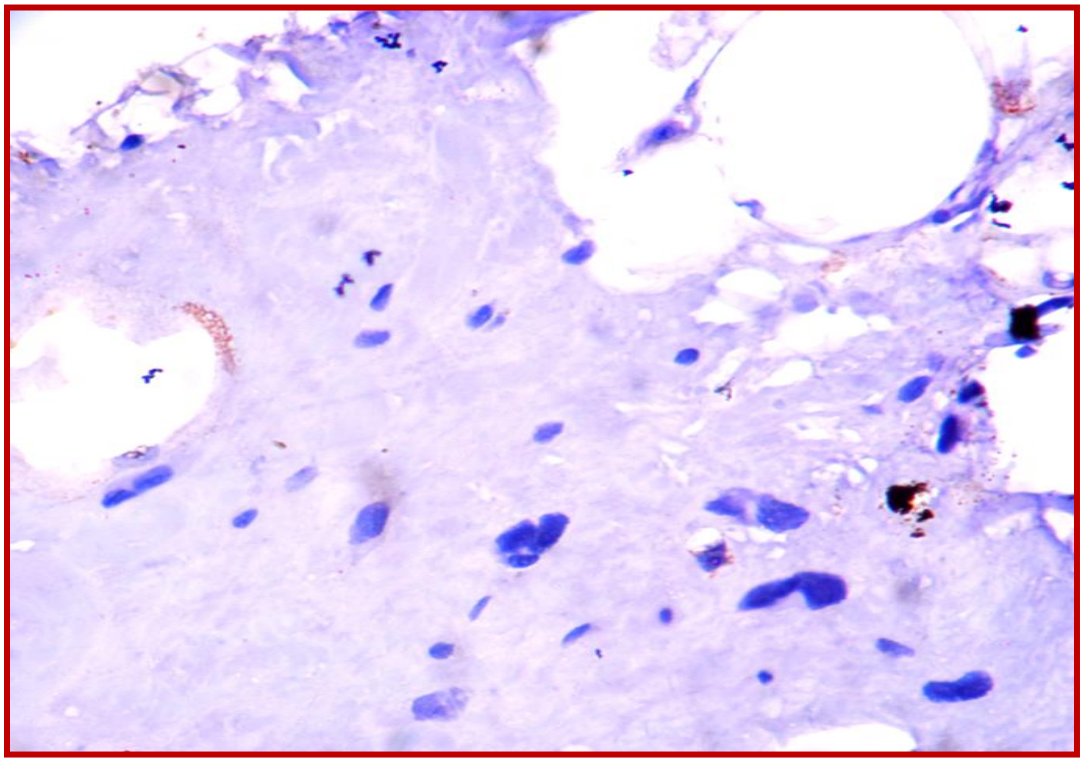

Figure 30- Well differentiated liposarcoma – IHC. Ki-67 score 1 and low index. Case 3595/15

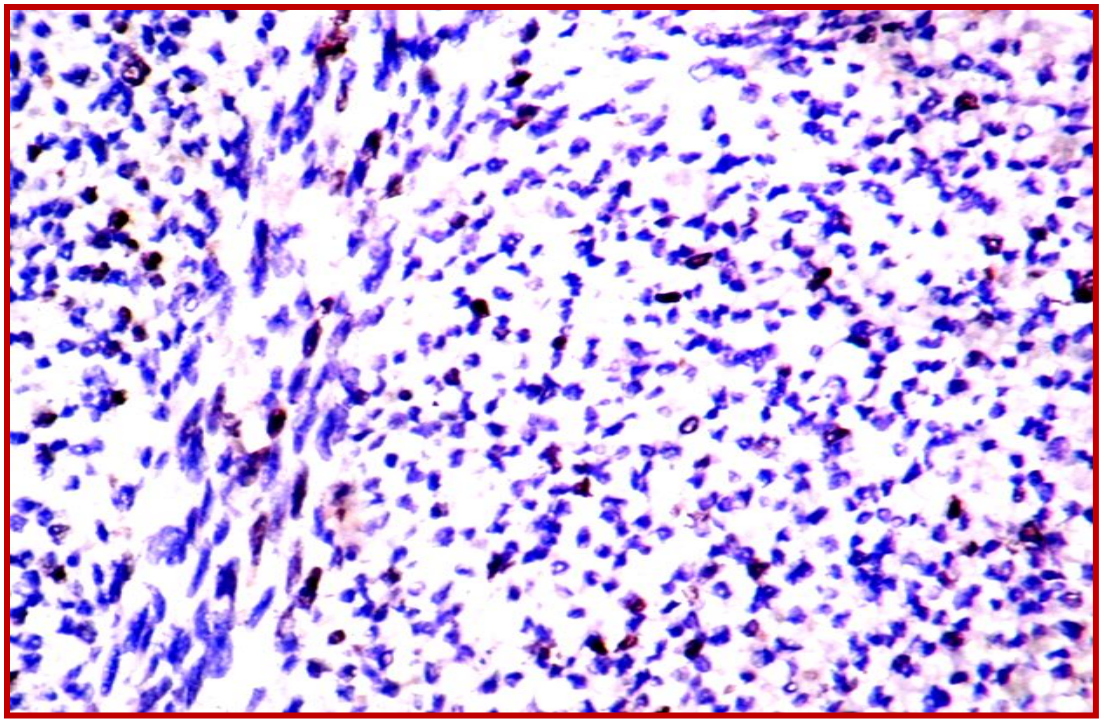

Figure 31 - Fibrosarcoma IHC. Ki-67 score 2 and high index. Case 1922/16

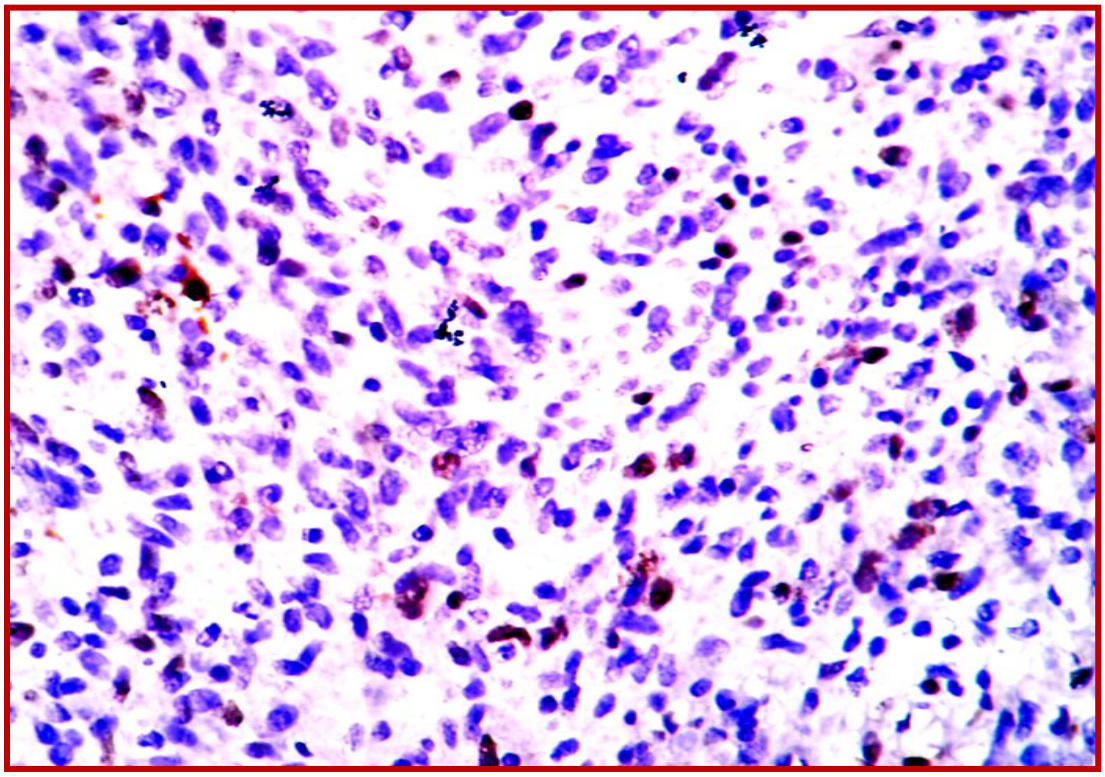

Figure 32- Infantile fibrosarcoma- IHC. Ki-67 score 2 and high index. Case 322/16

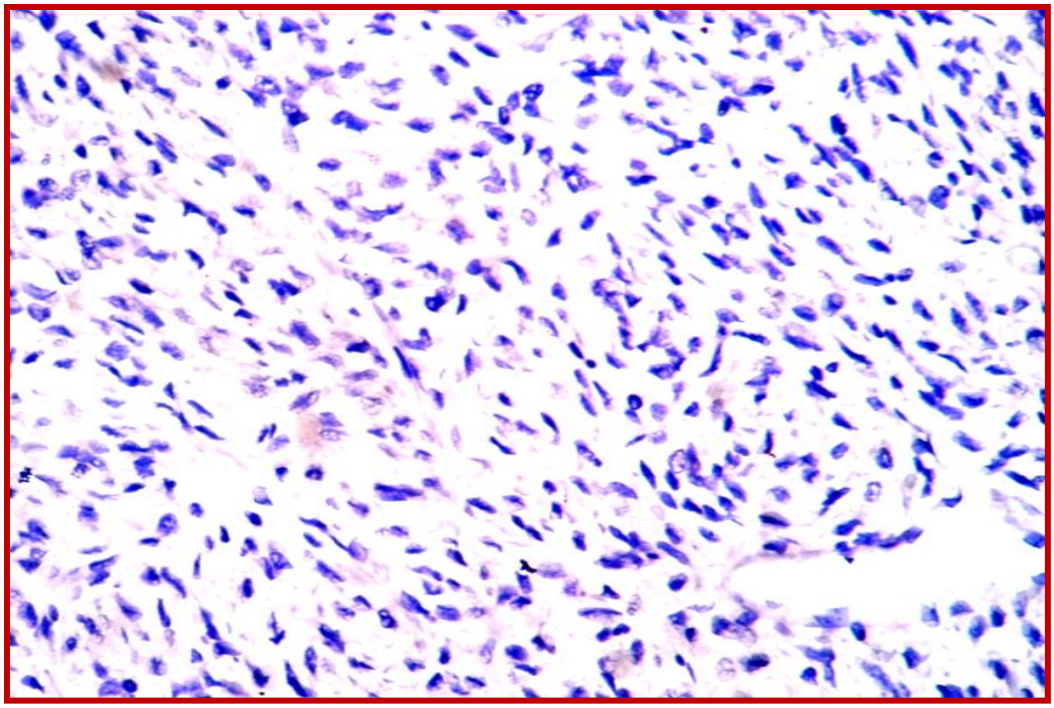

Figure 33 - Synovial sarcoma- IHC. Ki-67 score 1 and low index. Case 1194/15

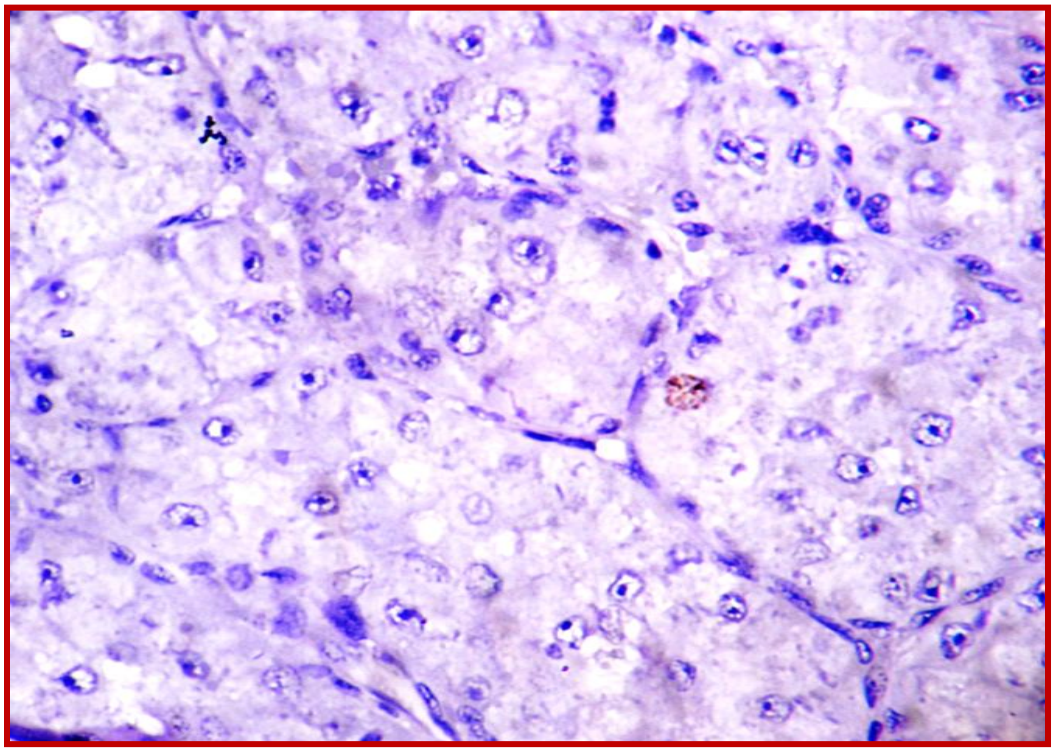

Figure 34 - Alveolar soft part sarcoma - IHC.Ki-67 score 1 and low index. Case 540/16

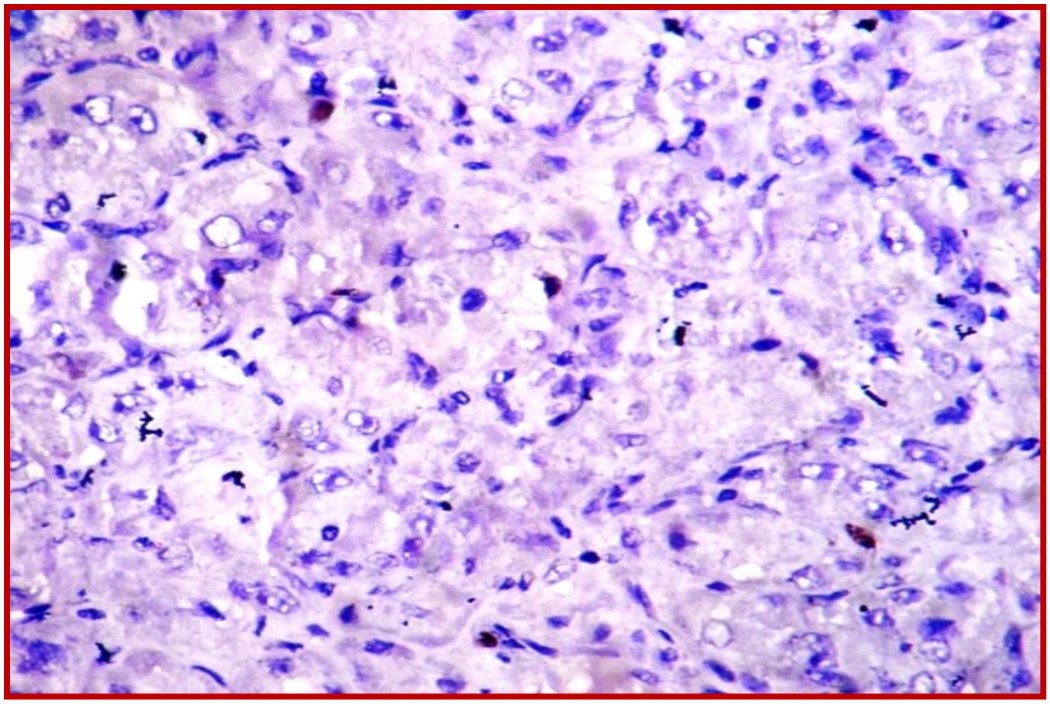

Figure 35 - Alveolar rhabdomyosarcoma- IHC. Ki-67 score 1 and low index. Case 1368/16

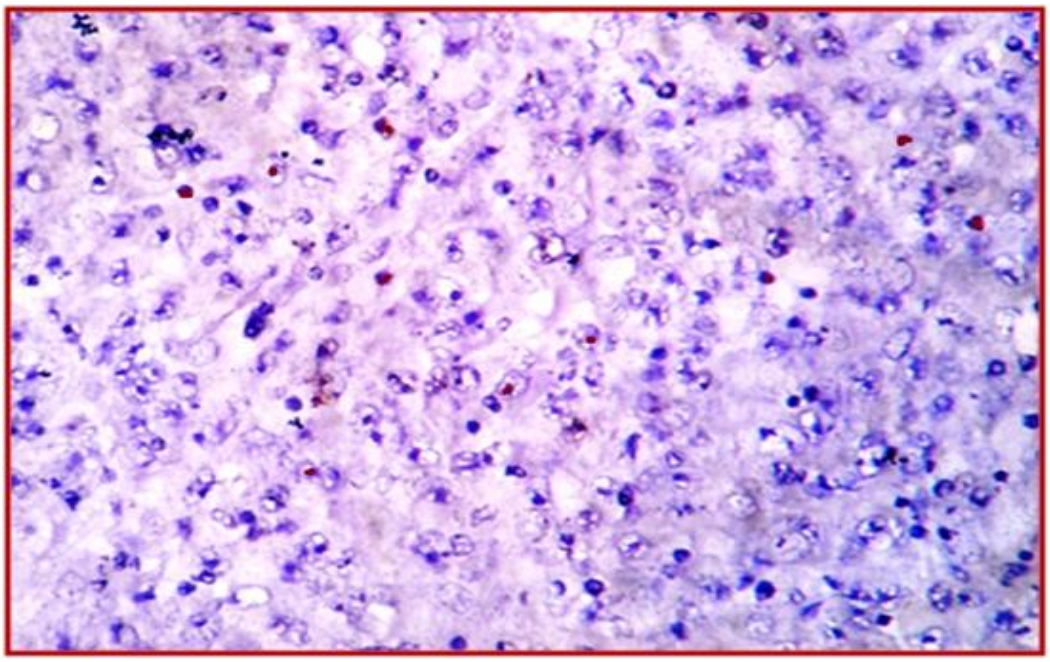

Figure 36 - MPNST - IHC. Ki-67 score 2 and high index. Case 1355/16

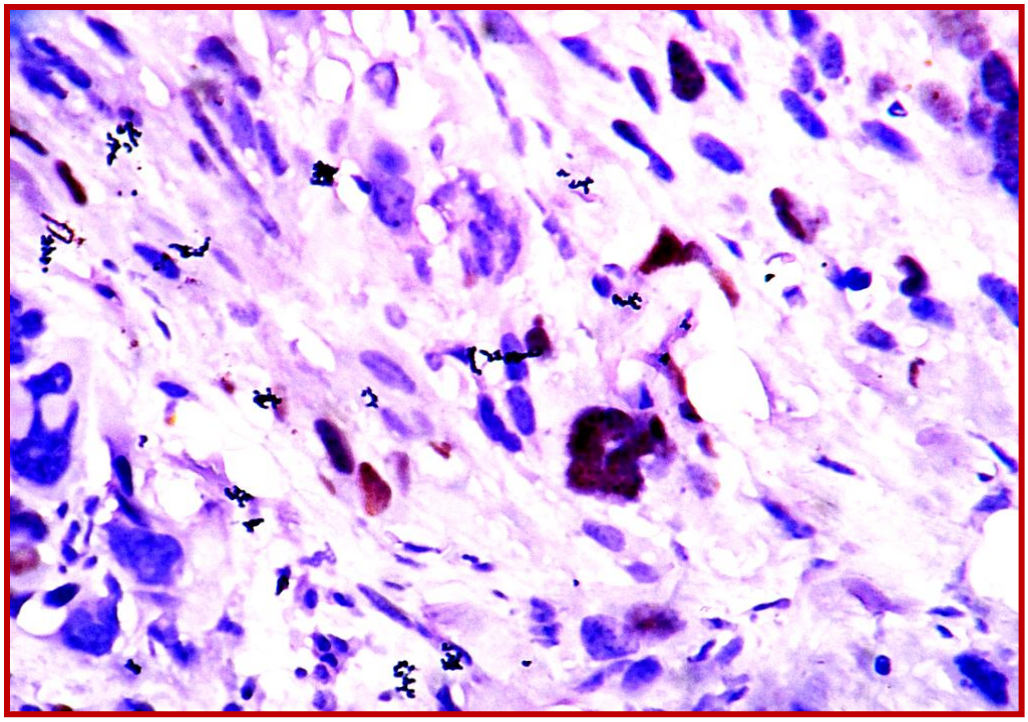

Figure 37- Undifferentiated pleomorphic sarcoma-IHC. Ki-67 score 2 and high index. Case 586/16

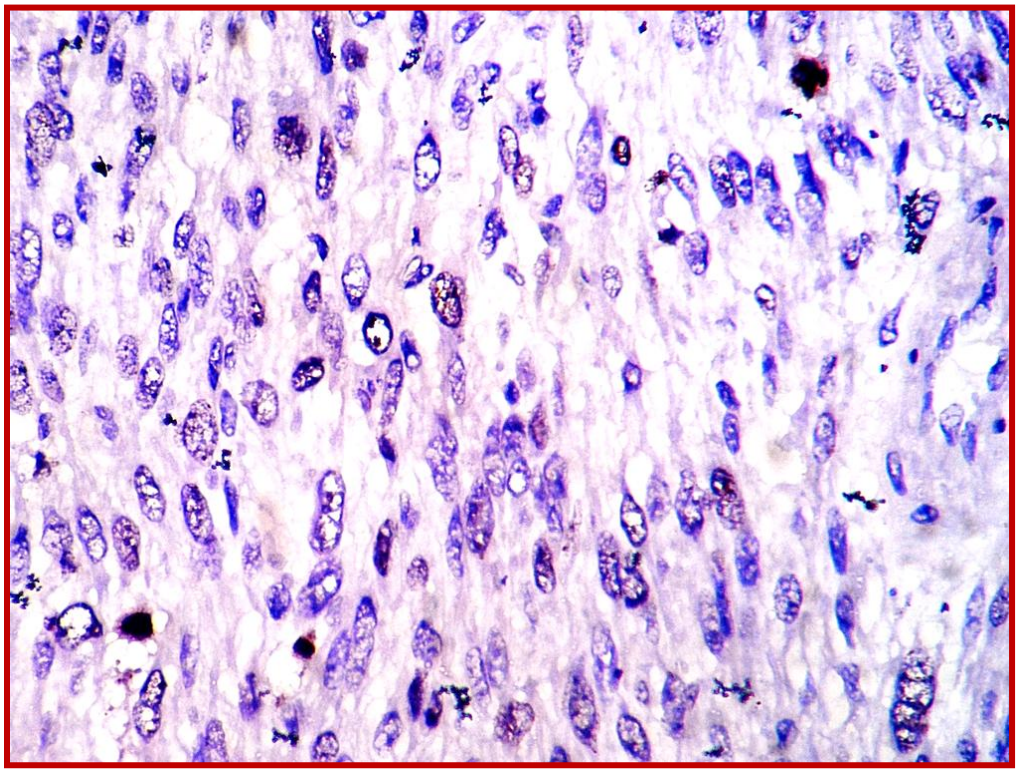

Figure 38 - Leiomyosarcoma-IHC. Ki-67 score 3 and high index. Case 304/16

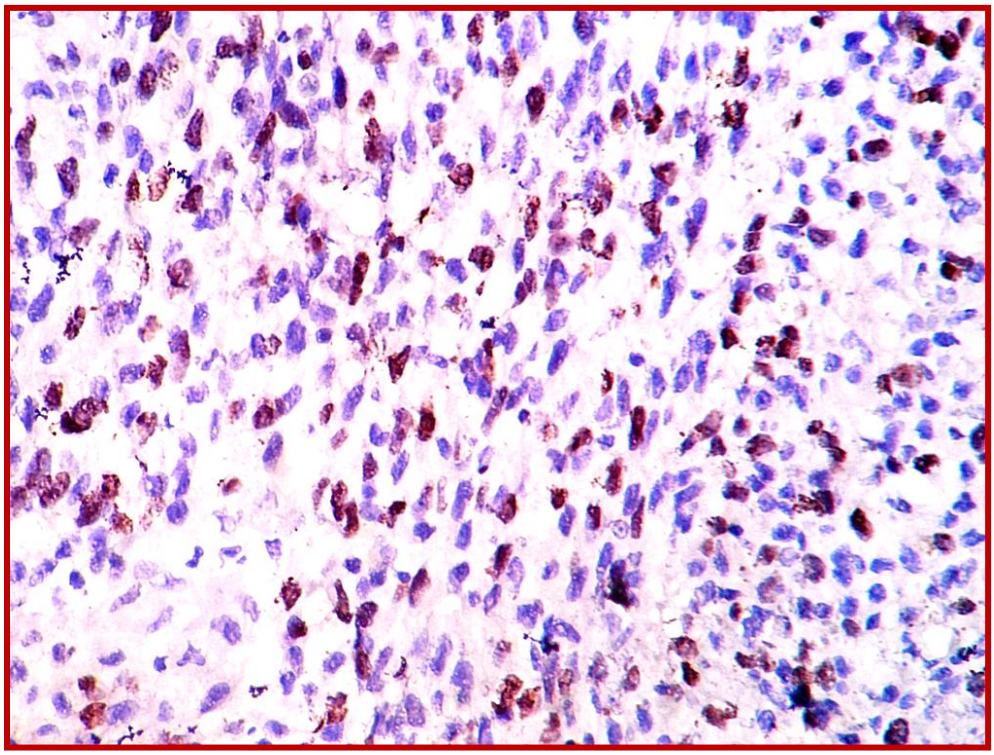

Figure 39 - Dedifferentiated liposarcoma- IHC. Ki-67 score 3 and high index. Case 108/16

DISCUSSION

DISCUSSION

Soft tissue tumours form a complex group composed of benign tumours, intermediate locally aggressive, intermediate rarely metastasizing and malignant tumours as emphasized by WHO 2013 classification[28]. These tumours have a wide variety of morphological patterns. Hence the present study has been undertaken to analyze the histopathological features of soft tissue tumours and their incidence in relation to age, sex and site.

Because of the lowest incidence of sarcomas among malignant neoplasms, there is difficulty in diagnosing and providing appropriate treatment for metastasis free survival especially in patients with high risk sarcomas. This has led to many studies with molecular genetics and immunohistochemistry all over the world. One among these prognostic markers used in our study to assess the proliferative potential and aggressiveness of sarcomas is Ki67. Ki67 expression by tumour cells is detected in paraffin embedded tissue sections of selected sarcomas with MIB-1 antibody. The study has attempted to establish the correlation between the histologic grade and Ki-67 index and efficiency of Immunohistochemical Ki-67 expression in assessing cellular proliferation and prognosis in sarcomas.

INCIDENCE OF SOFT TISSUE TUMOURS:

Incidence of soft tissue tumours in the present study was 1.3% of all neoplasms diagnosed in the department of pathology. (100/7750/2 years) which is comparable with studies by Mirza Asif Baig (2005)[12] where the overall incidence of soft tissue tumours was 1.6%.

TABLE 21 – COMPARISON OF FREQUENCY OF BENIGN AND MALIGNANT SOFT TISSUE TUMOURS

S.NO.	AUTHOR	NO.OF CASES	BENIGN	FREQUENCY (%)	MALIGNANT	FREQUENCY(%)	BENIGN: MALIGNANT RATIO
1	Myhre - Jensen O (1981)[52]	1403	1331	94.6%	72	5.4%	18.5:1
2	Kransdorf MJ (1995)[65]	31047	18677	60.2%	12370	39.8%	1.5:1
3	Mirza Asif Baig (2005)[12]	137	113	82.48%	24	17.52%	4.70:1
4	Agravat AH et al(2010)[140]	92	86	93.5%	6	6.5%	14.4:1
5	Bashar AH et al(2010)[141]	93	70	75.2%	23	24.8%	3:1

6	Vikas V Narhire et al (2012)[142]	154	138	89.6%	16	10.4%	8.6:1
7	Kinjal Bera et al (2015)[143]	131	122	93.13%	9	6.87%	13.5:1
8	Present study	100	50	50%	39	39%	1.3:1

In the present study, benign tumours (50%) were more common than malignant tumours (39%) with benign to malignant ratio of 1.3:1 which is comparable with Kransdorf MJ et al study (1995)[65] where the benign to malignant ratio was 1.5: 1 (Table 21).

AGE INCIDENCE OF SOFT TISSUE TUMOURS:

Most benign soft tissue tumours were seen in the age group of 20-50 years with the mean age of 35 years. Intermediate and malignant soft tissue tumours were commonly seen in the age group of 50-59 years with the mean age of 60 years. Similar results were observed by Batra et al (2013)[144] where benign tumours were common in the age group of 21-50 years and malignant tumours in 51-70 years age group. Kinjal Bera (2015)[143] also observed the age group of > 50 years common in malignant tumours which is similar to our study. The mean age of 35 years in

benign tumours is in correlation with studies by Kransdorf MJ et al (1995)[65,139] where the mean age of benign tumours was 35 years.

TABLE 22- COMPARISON OF SEXWISE INCIDENCE OF SOFT TISSUE TUMOURS

S.No.	STUDY	MALE:FEMALE RATIO	
		BENIGN	MALIGNANT
1	Geeta Dev et al (1974)[138]	1.7:1	2.4:1
2	Kransdorf MJ et al (1995)[65,139]	1.3:1	1.2:1
3	Mirza Asif Baig (2005)[12]	1.13:1	1:1
4	Janaki et al (2014)[145]	1.3:1	2:1
5	Present study	1:1	1.2:1

In the present study, the incidence of soft tissue tumours was slightly higher in males with male to female ratio of 1:0.9 which is comparable with studies by Myher Jensen (1981)[52] and Janaki et al (2014)[145] where the ratio was 1:1. Male to female ratio in benign tumours was 1:1 whereas in intermediate and malignant tumours, it was 1.2:1. This result is comparable with studies by Kransdorf et al (1995)[65,139] where male to female ratio was 1.3:1 in benign tumours and 1.2:1 in malignant tumours. (Table 22).

TABLE 23- COMPARISON OF SITE WISE DISTRIBUTION OF SOFT TISSUE TUMOURS

S.NO.	STUDY	BENIGN	MALIGNANT
1	Kransdorf MJ et al(1995)[65,139]	Upper extremity	Lower extremity
2	Mirza Asif Baig (2005)[12]	Head and neck and trunk	Lower extremity
3	Vikas V. Narhire et al (2012)[142]	Upper extremity	-
4	Batra et al (2013)[144]	Upper extremity	Lower extremity
5	Janaki et al (2014)[145]	Extremities	Lower extremity
6	Kinjal Bera et al (2015)[143]	Trunk (back)	Lower extremity
7	Present study	Upper extremity	Lower extremity

The sites of predilection in the present study were lower extremities (56%) for malignant tumours and upper extremities (36%) for benign soft tissue tumours. These results are comparable with studies conducted by Kransdorf et al (1995)[65,139], Batra et al (2013)[144] and Janaki et al (2015)[145]. Lower extremities were

the most common site involved in soft tissue tumours comparable with the above studies. (Table 23)

BENIGN SOFT TISSUE TUMOURS:

In the present study, Nerve sheath tumours (66%) were the most common benign soft tissue tumors followed by vascular tumours (12%). These results are comparable with studies conducted by Agravat AH et al (2010)[140], Bashar et al (2010)[141] and Vikas V. Narhire et al (2012)[142] where adipocytic tumours were the most common soft tissue tumours followed by vascular and peripheral nerve sheath tumours. (Table 24) .However in a study by Kinjal Bera et al (2015)[143], the second most common benign soft tissue tumour next to adipocytic tumours was neurofibroma. This is somewhat in correlation with the present study. The slight discrepancy in correlation with these studies is due to the exclusion of lipomas from our study.

Out of 50 benign tumours, the most common tumours in the present study were Neurofibromas (n=19) with male to female ratio of 1.1:1 and the mean age was 35 years. The most common site involved was upper extremity. Grossly, these tumours ranged in size from 1 to 20 cm with homogenous greyish white and myxoid appearance on cut section. Microscopically, the tumour had spindle shaped cells with buckled nuclei along with fibroblasts, perineurial cells and

lymphocytes.(Figure 1) which is comparable with studies by Kransdorf MJ (1995)[65] and Vikas V. Narhire (2012).[142]

TABLE 24- COMPARISON OF INCIDENCE OF MOST COMMON BENIGN SOFT TISSUE TUMOURS

S.NO.	STUDY	VASCULAR TUMOUR	NERVE SHEATH TUMOUR
1	Myhre Jensen o (1981)[52]	11.7%	-
2	Kransdorf MJ (1995)[65]	7.6%	13.5%
3	Agravat et al (2010)[140]	22.1%	20.9%
4	Bashar et al (2010)[141]	31.4%	11.4%
5	Vikas V Narhire (2012)[142]	20.2%	15.2%
6	Present study	12%	66%

Schwannomas (n=14) were more common in females with male to female ratio of 1:1.2 and occurred frequently in the third decade. The most common site involved was upper extremity and four cases were reported in the retroperitoneum. Grossly, these tumours ranged in size from 1 to 7 cm with greyish white and myxoid areas. Microscopically, they classically had both hypercellular areas with compactly arranged spindled cells exhibiting verrocay bodies and hypocellular myxoid areas (Figure 2a). One of the cases presented with mass in the retroperitoneum was

reported as Ancient Schwannoma because of the presence of extensive degenerative changes. (Figure 2b)

Next common group of tumours were haemangiomas (n=12). They were common in both second and fourth decades with scalp being the most commonly involved site. We had cases of both capillary and cavernous haemangiomas.

Among fibroblastic tumours, Benign fibrous histiocytoma was common (n=5) and frequently occurred in the age group of 20-29 years. Upper extremities were commonly involved. Grossly, these tumours were circumscribed with greyish white and orangish areas. Microscopically, tumour cells were spindle shaped arranged in fascicular and storiform pattern. Focal areas of histiocytic infiltration also were seen. This is comparable with studies by Fletcher et al (1990).[98] One of the cases was reported as cellular variant of Benign fibrous histiocytoma.(Figure 3)

Least common tumours encountered in the present study were leiomyoma (2%), glomangioma (1%), myxoma (1%), pleomorphic lipoma (1%) and juvenile hyaline fibromatosis (1%). Grossly, pleomorphic lipoma of the gluteal region was about 16x15x3.5 cm with yellowish and greyish white areas. Characteristic multinucleated floret giant cells with mature adipocytes in a mucoid stroma were seen. (Figure 4). This is comparable with studies by Enzinger FM and Shmookler (1981).[91,92]

In the present study, one year old female child presented with multiple swellings over the scalp. Grossly, the tumour was greyish white on cut section. Microscopically, the tumour was hypocellular with benign fibroblasts embedded in a dense hyalinised stroma (Figure 5). This case had the classical location and microscopic picture and was reported as Juvenile hyaline fibromatosis. This is in correlation with studies by Kitano et al (1972).[153]

INTERMEDIATE SOFT TISSUE TUMOURS:

Out of 11 intermediate soft tissue tumours, we had 4 cases of Dermatofibrosarcoma protuberans, 3 cases of well differentiated liposarcoma, 2 cases of fibromatosis and one case each of infantile fibrosarcoma and giant cell fibroblastoma. Dermatofibrosarcoma protuberans on cut section had greyish brown areas. (Figure 6). Microscopically, spindle shaped tumour cells were arranged in storiform pattern and extended into the subcutaneous fatty tissue. (Figure 7). This is comparable with studies by Gutirez et al (1984).[73]

Well differentiated liposarcoma on cut section was yellowish with greyish white areas (Figure 8). Lipoma-like variant was common in our study with mature adipocytes, atypical stromal cells and few lipoblasts. (Figure 9)

Infantile fibrosarcoma was reported in a case of one year male child with swelling in the hip region. It was characterized by round to ovoid and spindle shaped cells

with nuclear pleomorphism and mitotic activity. (Figure 10). This is comparable with studies by Enzinger FM et al (1976).[97]

SOFT TISSUE SARCOMAS:

TABLE 25- COMPARISON OF INCIDENCE OF SARCOMAS

DIAGNOSIS	HENRY J.MANKIN ET AL (2001)[146]	PRESENT STUDY
UPS	38.6%	28.20%
Liposarcoma	16.06%	17.95%
Synovial sarcoma	11.96%	17.94%
Fibrosarcoma	8.20%	15.38%
MPNST	7.13%	7.70%
Leiomyosarcoma	5.32%	5.13%
Rhabdomyosarcoma	2.62%	2.56%
Alveolar soft part sarcoma	1.07%	2.56%
Extraskeletal chondrosarcoma	0%	2.56%
Angiosarcoma	3.52%	0%
Epithelioid sarcoma	3.68%	0%
Clear cell sarcoma	1.8%	0%
TOTAL	100%	100%

Incidence of each subtype of soft tissue sarcoma in the present study is comparable with study by Henry J Mankin et al (2001)[146]. The incidence of UPS (the most

common), liposarcoma, synovial sarcoma, MPNST, leiomyosarcoma and rhabdomyosarcoma are in good correlation with the present study. (Table 25)

TABLE 26- COMPARATIVE ANALYSIS OF INCIDENCE OF UPS:

S.NO.	STUDY	UPS INCIDENCE
1	Kransdorf et al (1995)[139]	24%
2	Aydin et al (1999)[147]	22.8%
3	Henry J.Mankin et al (2001)[146]	38.6%
4	Krishnakanth et al (2014)[148]	16.66%
5	Mirza Asif Baig (2005)[12]	20.83%
6	Present study	28.20%

Undifferentiated pleomorphic sarcoma was the most common malignant soft tissue tumour in the present study (28.20%) followed by liposarcoma and synovial sarcoma (17.95%). This is in agreement with studies conducted by Kransdorf et al (1995)[139], Aydin et al (1999)[147], Henry J. Mankin et al(2001)[146], Mirza Asif Baig (2005)[12] and Krishnakanth et al (2014)[148] where undifferentiated pleomorphic sarcoma was the most common malignant tumour (Table 26)

TABLE 27- COMPARATIVE ANALYSIS OF FIRST COMMON UNDIFFERENTIATED PLEOMORPHIC SARCOMA:

S.NO.	STUDY	MEAN AGE	SEX RATIO	SITE
1	Sharan Weiss (1978)[149]	60 years	1.77:1	Lower extremity
2	Kransdorf MJ (1995)[139]	59 years	1.3:1	Lower extremity
3	Henry J Mankin (2001)[146]	58 years	1:1	Thigh
4	Mirza Asif Baig (2005)[12]	31.6 years	1.5:1	Lower extremity
5	Present study	54.2 years	1.8:1	Thigh

In the present study, undifferentiated pleomorphic sarcoma was the most common malignant soft tissue tumour with the mean age of 54.2 years and male to female ratio of 1.8:1. The site most commonly involved was thigh. These results are comparable with studies by Henry J Mankin (2001)[146], Kransdorf MJ (1995)[139] and Sharan Weiss (1978)[149]. (Table 27)

Grossly, the tumour was greyish white and firm with size ranging from 3 to 20 cm. (Figure 11). The most common subtype of undifferentiated pleomorphic sarcoma seen in the present study was storiform-pleomorphic type comparable with studies by Enzinger and Weiss (1978)[125] (Figure 12,13).

TABLE 28 – COMPARATIVE ANALYSIS OF SECOND COMMON LIPOSARCOMA:

S.NO.	STUDY	MEAN AGE	SEX RATIO	SITE
1	Geeta Dev et al (1974)[138]	60 years	3.2:1	Trunk
2	Pritchard (1978)[87]	34.5 years	1.5:1	Lower extremity
3	Kransdorf MJ (1995)[139]	52.3 years	1.3:1	Lower extremity
4	Henry J Mankin (2001[146])	57 years	1.3:1	Thigh
5	Mirza Asif Baig (2005)[12]	55 years	0.5:1	Thigh
6	Present study	54 years	2.5:1	Retroperitoneum

In the present study, the second most common malignant soft tissue tumour was liposarcoma with the mean age of 54 years and male to female ratio of 2.5:1. These

are in agreement with studies conducted by Geeta Dev et al (1974)[138], Kransdorf MJ et al (1995)[139] and Mirza Asif Baig (2005)[12].(Table 28). The most common site involved was the retroperitoneum in the present study which is not comparable with these studies.

The most common subtypes reported were myxoid liposarcoma (n=4) followed by dedifferentiated liposarcoma (n=3). Grossly, they ranged in size from 5 to 25 cm and were myxoid (Figure 14) and greyish white on cut section. Microscopically, myxoid liposarcoma had pleomorphic spindle shaped cells and lipoblasts in a myxoid stroma with delicate blood vessels. (Figure 15,16). One among them was high grade myxoid liposarcoma composed of round tumour cells with high grade nuclear atypia. (Figure 17) Dedifferentiated liposarcoma had lipogenic areas with abrupt transition to high grade sarcomatous areas. (Figure 18,19) These results were similar to studies by Reszel et al (1966).[67]

Among sarcomas of uncertain differentiation, majority were synovial sarcomas (n=7) which included three biphasic type and four spindle cell type sarcomas. (Figure 20). Males were commonly affected and the site commonly involved was the lower extremity. 29 year old female presented with swelling in the gluteal region had a solid grey white tumour of about 6x5 cm. Microscopy showed a tumour with polygonal to spindled tumour cells with abundant acidophilic cytoplasm arranged in alveolar pattern with central cellular dyscohesion and was

reported as Alveolar soft part sarcoma. (Figure 21,22). 50 year male with tumour in the gluteal region was diagnosed as Extraskeletal chondrosarcoma of myxoid type. (Figure 23).

Fibrosarcomas (n=6) had male to female ratio of 1:2 and mean age of 48 years. It also involved the lower extremity. Grossly,the tumour had greyish white to brown areas with extensive necrosis. (Figure 24). Microscopy revealed a tumour with pleomorphic spindled cells in a herring bone pattern. (Figure 25)

A case of alveolar rhabdomyosarcoma was reported in a 12 year old girl in the head and neck region with tumour cells arranged in alveolar pattern and separated by delicate vascular septa (Figure 26) which is similar to the study by Enzinger et al (1969).[117]

Three cases of malignant peripheral nerve sheath differentiation were in the present study which were common in females and involved upper extremities. Two of them were well differentiated and one was of epithelioid type. (Figure 27a,b)

Two cases of leiomyosarcoma were seen in males of more than 60 years involving the lower extremity. Grossly, the tumour was nodular and greyish white on cut section (Figure 28). Microscopically, the tumour cells were spindle shaped with blunt ended nuclei and scanty eosinophilic cytoplasm arranged in long fascicles. (Figure 29)

GRADING OF SOFT TISSUE SARCOMAS:

Soft tissue sarcomas were graded by FNCLCC (Federation Nationale des Centres de Lutte Contre le Cancer) grading system as proposed by Trojani et al (1984)[3]. The histologic features such as degree of differentiation, number of mitoses and volume of necrosis were thoroughly assessed to derive the grade of the sarcoma.

TABLE 29- COMPARATIVE ANALYSIS OF FNCLCC GRADE OF SOFT TISSUE SARCOMAS

S.NO.	STUDY	GRADE 1	GRADE 2	GRADE 3
1	Hiroshi Hashimoto et al (1992)[150]	15.52%	27.76%	56.71%
2	Aydin et al (1999)[147]	20%	34.3%	45.7%
3	Present study	21%	37%	42%

In the present study, most of the sarcomas were grade 3 (42%) followed by grade 2 (37%) and grade 1 (21%). This is comparable with studies by Hiroshi Hashimoto et al (1992)[150] and Aydin et al (1999)[147]. (Table 29)

KI 67 IMMUNOQUANTITATION:

In the present study, Ki-67 immunoquantitation revealed the following:

- Grade 1 sarcoma (Figure 30) shows low Ki-67 index (Score 1; 1-25%)
- Grade 2 sarcomas (Figure 31-35) show both low and high Ki-67 index. (Scores 2 and 3; 26-50% and >50%)
- Grade 3 sarcomas (Figure 36-39) show high Ki-67 index. (Score 3; >50%)

Spearman's Rho and Pearman's correlation coefficients were calculated. p value derived was 0.005 ($p<0.05$) and hence the correlation is strong and statistically significant.

These results are comparable with studies by Sahin et al (1991)[151], Aydin et al (1999)[147] and Sumiti Gupta et al (2015)[152] where they observed a very strong correlation between Ki-67 and histologic grade. Heslin et al (1989) also emphasized the importance of Ki-67 marker as an independent prognostic factor to determine the risk of distant metastasis and tumour related mortality[10].

SUMMARY

SUMMARY

In the present prospective study of 100 soft tissue tumours, the following results were obtained:

- Soft tissue tumours constituted only about 1.3% of all neoplasms during the study period.
- Benign tumours were more common than intermediate and malignant soft tissue tumours. Benign tumours constituted about 50% of cases, intermediate tumours about 11% and malignant tumours about 39%.
- The age range of soft tissue tumours was 1 to 80 years and the most common age group involved was 50-59 years.
- Soft tissue tumours were more common in males (52%)than females (48%) with male to female ratio of 1:0.9
- The sites of predilection were upper extremities for benign tumours and lower extremities for malignant tumours.
- Most common soft tissue tumours were peripheral nerve sheath tumours constituting about 36% of cases followed by fibroblastic tumours (15%).
- Most common benign soft tissue tumour was neurofibroma (19%) followed by schwannoma (14%) after excluding lipomas.

- Most common malignant soft tissue tumour was undifferentiated pleomorphic sarcoma (28%) followed by liposarcoma (17.95%) and synovial sarcoma (17.94%)
- Peripheral nerve sheath tumours were the most common soft tissue tumour group in both males and females.
- Undifferentiated pleomorphic sarcomas were more common in the sixth decade with male to female ratio of 1.8:1 and the site most commonly involved was thigh.
- Liposarcomas were more common in the sixth decade with male to female ratio of 2.5:1 and the site most commonly involved was retroperitoneum.
- In FNCLCC grading, most of the sarcomas were grade III (42%) followed by grade II (37%) and grade I (21%).
- 50% of grade III sarcomas were undifferentiated pleomorphic sarcomas.
- Ki-67 immunoquantitation results revealed grade 1 sarcomas with low index; grade 2 sarcomas with both high and low index and grade 3 sarcomas with high index.
- Statistical tests such as Spearman's rho and Pearman correlation coefficient tests indicated a very strong correlation between the histologic grade and Ki-67 index. p value was less than 0.05 and the study was statistically significant.

CONCLUSION

CONCLUSION

Soft tissue tumours are highly heterogenous group of tumours with diagnostic and therapeutic challenge. They are classified by WHO (2013) as benign, intermediate and malignant tumours based on their behaviour. They are further subclassified according to the specific lineage of differentiation due to a wide variety of histomorphological patterns.

Assessment of morphological prognostic factors most importantly the histologic grade is essential because of its usefulness in predicting the prognosis of soft tissue sarcomas. Due to advancement in molecular studies, Immunohistochemical expression of Ki-67 in sarcomas can be easily used to assess the cellular proliferation better than the mitotic score used in the grading system. Ki-67 antigen can be effectively used as an independent prognostic marker to assess the risk of distant metastasis and tumour related mortality. Based on Ki-67 labelling index, patients with high risk primary soft tissue sarcomas can be given adjuvant chemotherapy or radiotherapy for metastasis free survival in tertiary care centres.

ANNEXURES

ANNEXURE I

WHO CLASSIFICATION OF SOFT TISSUE TUMOURS (2013)

ADIPOCYTIC TUMOURS:

- **Benign**

  Lipoma

  Lipomatosis

  Lipomatosis of nerve

  Lipoblastoma / lipoblastomatosis

  Angiolipoma

  Myolipoma of soft tissue

  Chondroid lipoma

  Extra-renal angiomyolipoma

  Extra-adrenal myelolipoma

  Spindle cell / pleomorphic lipoma

  Hibernoma

- **Intermediate (locally aggressive)**

  Atypical lipomatous tumour / well differentiated liposarcoma

- **Malignant**

  Dedifferentiated liposarcoma

  Myxoid liposarcoma

  Pleomorphic liposarcoma

  Liposarcoma, not otherwise specified.

FIBROBLASTIC / MYOFIBROBLASTIC TUMOURS

- **Benign**

  Nodular fasciitis

  Proliferative fasciitis

  Proliferative myositis

  Myositis ossificans

  Fibro-osseous pseudotumour of digits

  Ischemic fasciitis

  Elastofibroma

  Fibrous hamartoma of infancy

  Fibromatosis colli

  Juvenile hyaline fibromatosis

  Inclusion body fibromatosis

  Fibroma of tendon sheath

  Desmoplastic fibroblastoma

  Mammary-type myofibroblastoma

  Calcifying aponeurotic fibroma

  Angiomyofibroblastoma

  Cellular angiofibroma

  Nuchal-type fibroma

  Gardner fibroma

  Calcifying fibrous tumour

- **Intermediate (locally aggressive)**

  Palmar / plantar fibromatosis

  Desmoid-type fibromatosis

  Lipofibromatosis

  Giant cell fibroblastoma

- **Intermediate (rarely metastasizing)**

  Dermatofibrosarcoma protuberans

  Fibrosarcomatous dermatofibrosarcoma protuberans

  Pigmented dermatofibrosarcoma protuberans

  Solitary fibrous tumour

  Solitary fibrous tumour, malignant

  Inflammatory myofibroblastic tumour

  Low grade myofibroblastic sarcoma

  Myxoinflammatory fibroblastic sarcoma / Atypical myxoinflammatory fibroblastic tumour

  Infantile fibrosarcoma

- **Malignant**

  Adult fibrosarcoma

  Myxofibrosarcoma

  Low-grade fibromyxoid sarcoma

  Sclerosing epithelioid fibrosarcoma

SO-CALLED FIBROHISTIOCYTIC TUMOURS

- **Benign**

  Tenosynovial giant cell tumour

  Localized type

  Diffuse type

  Malignant

  Deep benign fibrous histiocytoma

- **Intermediate (rarely metastasizing)**

  Plexiform fibrohistiocytic tumour

  Giant cell tumour of soft tissue

SMOOTH-MUSCLE TUMOURS

- **Benign**

  Leiomyoma of deep soft tissue

- **Malignant**

  Leiomyosarcoma (excluding skin)

PERICYTIC (PERIVASCULAR) TUMOURS

Glomus tumour (and variants)

Glomangiomatosis

Malignant glomus tumour

Myopericytoma

Myofibroma

Myofibromatosis

Angioleiomyoma

SKELETAL MUSCLE TUMOURS

Rhabdomyoma

Embryonal rhabdomyosarcoma

Alveolar rhabdomyosarcoma

Pleomorphic rhabdomyosarcoma

Spindle cell / Sclerosing rhabdomyosarcoma.

VASCULAR TUMOURS

- **Benign**

  Haemangioma

    Synovial

    Venous

    Arteriovenous haemangioma / malformation

  Epithelioid haemangioma

  Angiomatosis

  Lymphangioma

- **Intermediate (locally aggressive)**

  Kaposiform haemangioendothelioma

- **Intermediate (rarely metastasizing)**

  Retiform haemangioendothelioma

  Papillary intralymphatic angioendothelioma

  Composite haemangioendothelioma

  Pseudomyogenic (epithelioid sarcoma-like) haemangioendothelioma

  Kaposi sarcoma

- **Malignant**

  Epithelioid haemangioendothelioma

  Angiosarcoma of soft tissue

GASTROINTESTINAL STROMAL TUMOURS

Benign gastrointestinal stromal tumour

Gastrointestinal stromal tumour, uncertain malignant potential

Gastrointestinal stromal tumour, malignant

NERVE SHEATH TUMOURS

- **Benign**

  Schwannoma (including variants)

  Melanotic schwannoma

  Neurofibroma (including variants)

  Plexiform neurofibroma

  Perineurioma

  Malignant perineurioma

  Granular cell tumour

  Dermal nerve sheath myxoma

  Solitary circumscribed neuroma

  Ectopic meningioma

  Nasal glial heterotopia

  Benign Triton tumour

  Hybrid nerve sheath tumours

- **Malignant**

  Malignant peripheral nerve sheath tumour

  Epithelioid malignant nerve sheath tumour

  Malignant Triton tumour

  Malignant granular cell tumour

  Ectomesenchymoma

TUMOURS OF UNCERTAIN DIFFERENTIATION

- **Benign**

  Acral fibromyxoma

  Intramuscular myxoma (including cellular variant)

  Juxta-articular myxoma

Deep (“aggressive”) angiomyxoma

Pleomorphic hyalinizing angiectatic tumour

Ectopic hamartomatous thymoma

- **Intermediate (locally aggressive)**

Haemosiderotic fibrolipomatous tumour

- **Intermediate (rarely metastasizing)**

Atypical fibroxanthoma

Angiomatoid fibrous histiocytoma

Ossifying fibromyxoid tumour

Ossifying fibromyxoid tumour, malignant

Mixed tumour NOS

Mixed tumour NOS, malignant

Myoepithelioma

Myoepithelial carcinoma

Phosphaturic mesenchymal tumour, benign

Phosphaturic mesenchymal tumour, malignant

- **Malignant**

Synovial sarcoma NOS

Synovial sarcoma, spindle cell

Synovial sarcoma, biphasic

Epithelioid sarcoma

Alveolar soft-part sarcoma

Clear cell sarcoma of soft tissue

Extraskeletal myxoid chondrosarcoma

Extraskeletal Ewing sarcoma

Desmoplastic small round cell tumour

- Extra-renal rhabdoid tumour

Neoplasms with perivascular epithelioid cell differentiation (PEComa)

PEComa NOS, benign

PEComa NOS, malignant

Intimal sarcoma

UNDIFFERENTIATED / UNCLASSIFIED SARCOMAS

Undifferentiated spindle cell sarcoma

Undifferentiated pleomorphic sarcoma

Undifferentiated round cell sarcoma

Undifferentiated epithelioid sarcoma

Undifferentiated sarcoma NOS

ANNEXURE II

PROFORMA

HISTOPATHOLOGICAL STUDY OF SOFT TISSUE TUMOURS AND CORRELATION OF HISTOLOGIC GRADE OF SOFT TISSUE SARCOMAS WITH PROLIFERATIVE MARKER KI 67 IN SELECTED CASES

Name:

Age/Sex:

IP No.:

HPE No.:

H/O presenting illness:

Significant past history (if any):

Type of specimen:

Anatomical site:

Laterality:

Details of any neo-adjuvant therapy:

Details of any relevant imaging (soft tissue sarcomas):

Details of any investigation for metastatic workup:

Clinical /differential diagnosis:

Operative findings-plane of tumour:

Gross findings:

- Specimen and tumour measurement
- Distance from tumour to closest margin
- Nature of tissue between tumour and margin (fat/muscle/fascia)
- Nature of the tumour interface with normal tissue (infiltrative/well circumscribed)
- Cut section appearance – haemorrhage present or absent
- Necrosis : if present –estimated % of tumour volume
- Number of Lymph nodes identified

Microscopic findings:

- Tumor site
- Depth – tissue plane

  Superficial

  Dermal

  Subcutaneous

  Deep

  Fascial

  Subfascial

  Intramuscular

  Mediastinal

  Intraabdominal

  Retroperitoneal

  Other (specify)
- Tumour description – cellularity, pleomorphism

- Mitotic count - /10 HPF
- Necrosis - % of tumour volume
- Distance from close surgical margins
- Histologic typing (WHO)
- Vascular invasion if any
- Lymph node involved by tumour out of total nodes resected

Tumour grading (FNCLCC):

- Differentiation score
- Mitotic index score
- Tumour cell necrosis
- Total tumour score

Grade:

Grading not possible/applicable:

AJCC tumour stage (TNGM):

Immunohistochemistry if applicable (Ki-67):

Ki-67 score and index

ANNEXURE III

HAEMATOXYLIN AND EOSIN STAINING METHOD

1. Sections will be deparaffinised with xylene for 20 minutes.

2. Sections will be hydrated through descending concentrations (absolute alcohol, 90%, 70%, 50%) of ethanol to water solutions.

3. Sections will be rinsed in distilled water.

4. Sections will be placed in Ehrlich haematoxylin stain for 20-30 minutes.

5. Sections will be rinsed with water.

6. Differentiation will be done by immersing the sections in 1% acid alcohol for 10 seconds.

7. Sections will be rinsed with water.

8. Blueing will be done by keeping the sections in Scott's tap water for 2-10 minutes.

9. Counterstaining will be done with 1% aqueous Eosin for 1-3 minutes.

10. Sections will be rinsed with water.

11. Sections will be dehydrated through increasing concentrations of ethanol solutions (50%, 70%, 95%, absolute alcohol) and cleared with xylene.

12. Sections will be mounted with DPX.

ANNEXURE IV

KEY TO MASTER CHART

SEX:

M - Male

F - Female

HPE NO – Histopathological Examination Number

LATERALITY:

R – Right L – Left

DIFFERENTIATION SCORE:

1 – Sarcoma with close resemblance to normal adult mesenchymal tissue

2 – Sarcoma with certain histologic typing

3 – Undifferentiated / unclassified sarcomas, sarcomas of uncertain type.

MITOSIS SCORE:

1 – 0-9 mitoses/ 10 HPF

2 – 10-19 mitoses/ 10 HPF

3 – 20 or more mitoses/ 10 HPF

NECROSIS SCORE:

0 – No necrosis

1 – 50% or less necrosis

2 – more than 50% necrosis

TOTAL SCORE:

2 and 3 – Grade 1

4 and 5 – Grade 2

6, 7 and 8 – Grade 3

ANNEXURE VA

MASTER CHART OF HISTOPATHOLOGY OF SOFT TISSUE TUMOURS

S.NO	AGE	SEX	IP NO	SITE	LATERALITY	HPE NO	TUMOUR SIZE	DIAGNOSIS
1	29	M	50801	Arm	R	3238/14	8.5x5x4 cm	Benign fibrous histiocytoma
2	17	F	48812	Supraorbital region	R	3284/14	3.5x2x0.5 cm	Neurofibroma
3	40	M	115645	Arm	L	3342/14	3.5x2.5x1 cm	Benign fibrous histiocytoma
4	60	F	49454	Retroperitoneum	L	3394/14	8.5x8x5 cm	Undifferentiated Pleomorphic sarcoma
5	17	M	129726	Forearm	R	3627/14	4.5x3.5x1.5cm	Capillary haemangioma
6	48	M	61673	Hand	R	3747/14	3x2x1 cm	Neurofibroma
7	21	F	58218	Arm	L	3804/14	13x9x5 cm	Fibrosarcoma
8	45	F	70722	Leg	L	3862/14	20x15x3 cm	Synovial Sarcoma
9	30	M	66595	Thigh	R	3985/14	3x2.5x2 cm	Undifferentiated Pleomorphic sarcoma
10	30	F	64606	Elbow	L	4069/14	3.5x3.5x2 cm	Malignant peripheral nerve sheath tumour
11	17	M	66840	Temporal region	L	4109/14	5x3.5x2.5 cm	Neurofibroma
12	40	F	61538	Retroperitoneum	R	4146/14	6x5x4.5 cm	Ancient Schwannoma
13	50	F	64634	Scalp	R	4401/14	8x7.5x4 cm	Dermatofibrosarcoma protuberans
14	32	F	190261	Scalp	L	4419/14	1.5x1x0.5 cm	Pyogenic granuloma
15	20	M	71905	Axilla	R	4437/14	9x6x3 cm	Neurofibroma
16	20	F	7513	Gluteal region	L	356/15	4.5X3x1.5 cm	Benign fibrous histiocytoma
17	32	F	4797	Leg	L	368/15	10x6x1.5 cm	Haemangioma
18	59	F	18400	Forearm	L	448/15	12x8.5x5.5 cm	Synovial Sarcoma
19	39	M	5837	Retroperitoneum	L	520/15	7x5.5x2 cm	Schwannoma
20	40	M	24596	Scalp	L	560/15	2x1x0.5 cm	Capillary haemangioma
21	50	M	10168	Thigh	L	597/15	9x8x5 cm	Fibrosarcoma
22	29	F	1307	Forehead	R	598/15	1.5x1x1 cm	Benign fibrous histiocytoma
23	24	M	13920	Arm	L	622/15	5.5x5x1 cm	Neurofibroma
24	41	M	13659	Gluteal region	R	636/15	3x3x2 cm	Myxoma
25	55	F	73064	Thigh	L	786/15	8x6.5x2 cm	Malignant peripheral nerve sheath tumour

26	80	M	16483	Thigh	L	898/15	4x3x2 cm	Undifferentiated Pleomorphic sarcoma
27	60	F	15372	Chest wall	R	927/15	13x8x5 cm	Dermatofibrosarcoma protuberans
28	40	F	755045	Forearm	L	934/15	2x1.5x0.5 cm	Neurofibroma
29	37	M	30223	Arm	L	1075/15	4x4x2 cm	Dermatofibrosarcoma protuberans
30	65	M	20750	Leg	R	1127/15	16x12.5x5.5 cm	Undifferentiated Pleomorphic sarcoma
31	79	M	30886	Thigh	L	1165/15	14x12x9 cm	Atypical lipomatous neoplasm
32	44	M	20270	Thigh	R	1194/15	13x10.5x10 cm	Synovial Sarcoma
33	8	Mch	38535	Neck	L	1318/15	6x4x2 cm	Neurofibroma
34	53	F	6548	Leg	L	1383/15	15x10x4.5 cm	Undifferentiated Pleomorphic sarcoma
35	50	F	39434	Inguinal region	R	1503/15	9x5.5x4.5 cm	Dermatofibrosarcoma protuberans
36	26	F	40873	Forearm	R	2653/15	4x3.5x2.5 cm	Schwannoma
37	50	M	36322	Retroperitoneum	L	1608/15	20x15x12 cm	Undifferentiated Pleomorphic sarcoma
38	54	M	42504	Inguinal region	R	1691/15	10x8x6 cm	Dedifferentiated liposarcoma
39	55	M	43263	Thigh	R	1742/15	3x2.5x1.5 cm	Schwannoma
40	65	F	1054680	Leg	L	1900/15	2.5x2x1.5 cm	Schwannoma
41	32	M	1053175	Retroperitoneum	L	1909/15	6.5x4.5x2 cm	Schwannoma
42	27	F	1054980	Retroperitoneum	L	1022/15	7x6.5x1 cm	Schwannoma
43	20	M	6839	Thigh	L	2042/15	20x19x11 cm	Neurofibroma
44	55	F	1055374	Retroperitoneum	L	2061/15	35x30x15 cm	Well differentiated liposarcoma
45	32	M	133564	Foot	R	2140/15	4x3x2.5 cm	Synovial Sarcoma
46	60	F	1058384	Thigh	R	2173/15	6.5x5.5x3.5 cm	Fibrosarcoma
47	70	M	1059886	Leg	R	2343/15	10x8x3 cm	Synovial Sarcoma
48	45	F	1055368	Arm	L	2358/15	5.5x4x2 cm	Schwannoma
49	18	M	44823	Arm	R	2439/15	5x4x2 cm	Neurofibroma
50	27	F	106400	Hand	R	2523/15	2x1.5x1 cm	Schwannoma
51	56	M	25760	Leg	L	2632/15	2x1x0.5 cm	Glomangioma

52	32	F	1069511	Neck	R	2643/15	2x2x1.5 cm	Schwannoma
53	47	M	1066778	Thigh	R	2668/15	9.5x9x8 cm	Undifferentiated Pleomorphic sarcoma
54	63	M	1068104	Thigh	L	2694/15	6x6x4 cm	Leiomyosarcoma
55	18	F	1072097	Thigh	L	2711/15	6.5x3x2 cm	Cavernous haemangioma
56	49	F	1068936	Foot	L	2803/15	6x5x5 cm	Synovial Sarcoma
57	40	F	1066319	Leg	R	2833/15	9.5x9x5 cm	Undifferentiated Pleomorphic sarcoma
58	50	M	11688	Gluteal region	L	2911/15	5x2x1 cm	Extraskeletal myxoid chondrosarcoma
59	55	F	1067146	Retroperitoneum	R	2930/15	16x14x9 CM	Leiomyoma
60	60	M	1080107	Thigh	R	3237/15	10x7x6 cm	Undifferentiated Pleomorphic sarcoma
61	48	M	229302	Infraclavicular region	R	3286/15	5x2.5x2 cm	Giant cell fibroblastoma
62	27	M	248156	Wrist	L	3338/15	1x1x0.5 cm	Schwannoma
63	40	M	1076204	Retroperitoneum	L	3358/15	11x10x5 cm	Dedifferentiated liposarcoma
64	33	M	1083039	Axilla	L	3415/15	7x6x3 cm	Leiomyoma
65	35	F	1083043	Shoulder	L	3493/15	3x3x2.5 cm	Fibromatosis
66	65	M	1083754	Gluteal region	L	3595/15	7x6x2 cm	Well differentiated liposarcoma
67	48	M	61673	Hand	R	2537/15	3x2x1 cm	Neurofibroma
68	49	F	1089893	Neck	R	3764/15	4x1.5x1.5 cm	Neurofibroma
69	53	M	1092520	Gluteal region	L	60/16	16x15x3.5 cm	Pleomorphic lipoma
70	44	F	1094720	Gluteal region	R	88/16	2.5x2x1 cm	Neurofibroma
71	55	M	1092571	Thigh	R	92/16	3x2x1 cm	Synovial Sarcoma
72	78	F	1092584	Gluteal region	R	102/16	18x17x4 cm	Myxoid Liposarcoma
73	56	M	108995	Hand	R	108/16	5.5x5x3 cm	Dedifferentiated liposarcoma
74	20	F	1094166	Arm	R	119/16	10x5.5x2 cm	Neurofibroma
75	62	F	760	Hand	R	302/16	4x3.5x2 cm	Schwannoma
76	70	M	1093095	Leg	R	304/16	14x12x3 cm	Leiomyosarcoma
77	46	M	1096703	Thigh	L	307/16	17x15x7 cm	Myxoid Liposarcoma

78	1	M	99351	Hip	L	322/16	6x4.5x2 cm	Infantile fibrosarcoma
79	52	F	1096675	Leg	R	378/16	8x7.5x4 cm	Fibrosarcoma
80	45	F	29279	Leg	L	431/16	2x2x1 cm	Neurofibroma
81	47	F	2619	Wrist	L	534/16	1.5x1.5x1 cm	Schwannoma
82	29	F	1101391	Gluteal region	R	540/16	6x5x3 cm	Alveolar soft part sarcoma
83	39	M	1100085	Chest wall	R	586/16	5x4.5x3.5 cm	Undifferentiated Pleomorphic sarcoma
84	72	F	1100824	Gluteal region	L	761/16	3.5x3x2 cm	Undifferentiated Pleomorphic sarcoma
85	56	F	1112145	Arm	L	973/16	3x2.5x1.5 cm	Schwannoma
86	26	M	1112728	Leg	L	1024/16	2.5x2x1 cm	Neurofibroma
87	60	M	111164	Arm	L	1087/16	5x5x4 cm	Fibrosarcoma
88	26	M	1115909	Submental region	L	1115/16	4x2.5x2 cm	Neurofibroma
89	54	M	1010322	Scalp	R	1147/16	2x1.5x1 cm	Capillary haemangioma
90	57	F	1114158	Arm	L	1355/16	8.5x6x4.5 cm	Malignant peripheral nerve sheath tumour
91	42	F	28394	Forearm	R	1365/16	1x1x0.5 cm	Neurofibroma
92	12	F	117731	Submental region	R	1368/16	4.5x3.5x2.5 cm	Alveolar rhabdomyosarcoma
93	23	F	1119093	Face	L	1384/16	10x5x4.5 cm	Neurofibroma
94	52	M	117859	Leg	L	1414/16	4.5x3.5x2.5 cm	Neurofibroma
95	55	M	4043184	Foot	L	1453/16	7.5x6x3 cm	Myxoid liposarcoma
96	47	F	1128872	Thigh	L	1922/16	7.5x5x3.5 cm	Fibrosarcoma
97	50	F	1113109	Retroperitoneum	R	2044/16	25x20x12 cm	Myxoid Liposarcoma
98	5	M	1131658	Gluteal region	L	2119/16	6x4x1.5 cm	Fibromatosis
99	1	Fch	139762	Scalp	R	2199/16	6x4x1 cm	Juvenile hyaline fibromatosis
100	24	M	1096704	Hand	L	2326/16	4x1.5x1 cm	Benign fibrous histiocytoma

ANNEXURE VB

MASTER CHART OF FNCLCC GRADING OF SOFT TISSUE SARCOMAS

S. NO	AGE	SEX	HPE NO	SIZE	DIAGNOSIS	DIFFERENTIATION SCORE	MITOSIS SCORE	NECROSIS SCORE	TOTAL SCORE	GRADE
1	60	F	3394/14	8.5x8x5 cm	Undifferentiated Pleomorphic sarcoma	2	2	1	5	2
2	21	F	3804/14	13x9x5 cm	Fibrosarcoma	1	1	0	2	1
3	45	F	3862/14	20x15x3 cm	Synovial Sarcoma	3	1	0	4	2
4	30	M	3985/14	3x2.5x2 cm	Undifferentiated Pleomorphic sarcoma	3	3	1	7	3
5	30	F	4069/14	3.5x3.5x2 cm	Malignant peripheral nerve sheath tumour	1	1	0	2	1
6	59	F	448/15	12x8.5x5.5 cm	Synovial Sarcoma	3	1	1	5	2
7	50	M	597/15	9x8x5 cm	Fibrosarcoma	2	1	1	4	2
8	55	F	786/15	8x6.5x2 cm	Malignant peripheral nerve sheath tumour	2	3	2	7	3
9	80	M	898/15	4x3x2 cm	Undifferentiated Pleomorphic sarcoma	2	2	1	5	2
10	65	M	1127/15	16x12.5x5.5 cm	Undifferentiated Pleomorphic sarcoma	3	3	1	7	3
11	79	M	1165/15	14x12x9 cm	Atypical lipomatous neoplasm	1	1	0	2	1
12	44	M	1194/15	13x10.5x10 cm	Synovial Sarcoma	3	1	0	4	2
13	53	F	1383/15	15x10x4.5 cm	Undifferentiated Pleomorphic sarcoma	3	3	2	8	3
14	50	M	1608/15	20x15x12 cm	Undifferentiated Pleomorphic sarcoma	2	2	2	6	3
15	54	M	1691/15	10x8x6 cm	Dedifferentiated liposarcoma	3	3	2	8	3
16	55	F	2061/15	35x30x15 cm	Well differentiated liposarcoma	1	1	0	2	1
17	32	M	2140/15	4x3x2.5 cm	Synovial Sarcoma	3	1	0	4	2

18	60	F	2173/15	6.5x5.5x3.5 cm	Fibrosarcoma	2	2	1	5	2
19	70	M	2343/15	10x8x3 cm	Synovial Sarcoma	3	2	0	5	2
20	47	M	2668/15	9.5x9x8 cm	Undifferentiated Pleomorphic sarcoma	2	3	1	6	3
21	63	M	2694/15	6x6x4 cm	Leiomyosarcoma	1	1	1	3	1
22	49	F	2803/15	6x5x5 cm	Synovial Sarcoma	3	2	3	8	3
23	40	F	2833/15	9.5x9x5 cm	Undifferentiated Pleomorphic sarcoma	3	3	1	7	3
24	50	M	2911/15	5x2x1 cm	Extraskeletal myxoid chondrosarcoma	3	1	0	4	2
25	60	M	3237/15	10x7x6 cm	Undifferentiated Pleomorphic sarcoma	3	3	2	8	3
26	40	M	3358/15	11x10x5 cm	Dedifferentiated liposarcoma	3	2	1	6	3
27	65	M	3595/15	7x6x2 cm	Well differentiated liposarcoma	1	1	0	2	1
28	55	M	92/16	3x2x1 cm	Synovial Sarcoma	3	1	0	4	2
29	78	F	102/16	18x17x4 cm	Myxoid Liposarcoma	2	1	0	3	1
30	56	M	108/16	5.5x5x3 cm	Dedifferentiated liposarcoma	3	3	1	7	3
31	70	M	304/16	14x12x3 cm	Leiomyosarcoma	2	3	1	6	3
32	46	M	307/16	17x15x7 cm	Myxoid Liposarcoma	2	1	0	3	1
33	1	M	322/16	6x4.5x2 cm	Infantile fibrosarcoma	2	3	0	5	2
34	52	F	378/16	8x7.5x4 cm	Fibrosarcoma	1	1	0	2	1
35	29	F	540/16	6x5x3 cm	Alveolar soft part sarcoma	3	1	0	4	2
36	39	M	586/16	5x4.5x3.5 cm	Undifferentiated Pleomorphic sarcoma	3	2	1	6	3
37	72	F	761/16	3.5x3x2 cm	Undifferentiated Pleomorphic sarcoma	3	3	1	7	3
38	60	M	1087/16	5x5x4 cm	Fibrosarcoma	2	3	1	6	3
39	57	F	1355/16	8.5x6x4.5 cm	Malignant peripheral nerve sheath tumour	3	2	1	6	3

40	12	F	1368/16	4.5x3.5x2.5 cm	Alveolar rhabdomyosarcoma	3	2	0	5	2
41	55	M	1453/16	7.5x6x3 cm	Myxoid liposarcoma	3	3	1	7	3
42	47	F	1922/16	7.5x5x3.5 cm	Fibrosarcoma	1	2	1	4	2
43	50	F	2044/16	25x20x12 cm	Myxoid Liposarcoma	2	1	0	3	1

ANNEXURE VI

LIST OF ABBREVAITIONS USED

AFIP - Armed Forces Institute of Pathology

AJCC - American Joint Committee on Cancer

CD - Cluster of Differentiation

CDK - Cyclin Dependent Kinase

CK - Cyto Keratin

DFSP - DermatoFibroSarcoma Protuberans

DSS - Disease Specific Survival

EMA - Epithelial Membrane Antigen

FFPE - Formalin Fixed Paraffin Embedded

FLI 1 - Friend Leukemia Integration 1 transcription factor

FNA - Fine Needle Aspiration

FNCLCC - Federation Nationale des Centres de Lutte Contre le Cancer

HMB - Human Melanoma Black

HPF - High Power Field

IHC - ImmunoHistoChemistry

LMS - Leiomyosarcoma

MDM2 - Mouse Double Minute 2 homolog

MIB1 - Mindbomb 1 (E3 ubiquitin protein ligase)

MPNST - Malignant Peripheral Nerve Sheath Tumour

MSKCC - Memorial Sloan-Kettering Cancer Center

NCI - National Cancer Institute

PNET - Primitive Neuro Ectodermal Tumour

RMS - RhabdoMyoSarcoma

SIN - Size, vascular Invasion, Necrosis

SSG - Scandinavian Sarcoma Group

STS - Soft Tissue Sarcoma

STT - Soft Tissue Tumour

TNGM - Tumour Node Grade Metastasis

UPS - Undifferentiated Pleomorphic Sarcoma

WHO - World Health Organisation

ANNEXURE – VII

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ANNEXURE VIII

INSTITUTION ETHICAL COMMITTEE APPROVAL

MADURAI MEDICAL COLLEGE

MADURAI, TAMILNADU, INDIA -625 020

(Affiliated to The Tamilnadu Dr.MGR Medical University, Chennai, Tamil Nadu)

ETHICS COMMITTEE

CERTIFICATE

Name of the Candidate	:	Dr. S.RAASI
Course	:	PG in M.D., PATHOLOGY
Period of Study	:	2014-2017
College	:	MADURAI MEDICAL COLLEGE
Research Topic	:	**HISTOPATHOLOGICAL STUDY OF SOFT TISSUE TUMOURS AND ASSESSMENT OF PROGNOSTIC FACTORS IN SOFT TISSUE SARCOMAS WITH IMMUNO HISTOCHEMICAL MARKERS.**

The Ethics Committee, Madurai Medical College has decided to inform that your Research proposal is accepted.

Member Secretary

23 SEP 2015

Dean / Convenor

Dean
Madurai Medical College
Madurai-20

ANNEXURE IX

ANTI-PLAGIARISM CERTIFICATE

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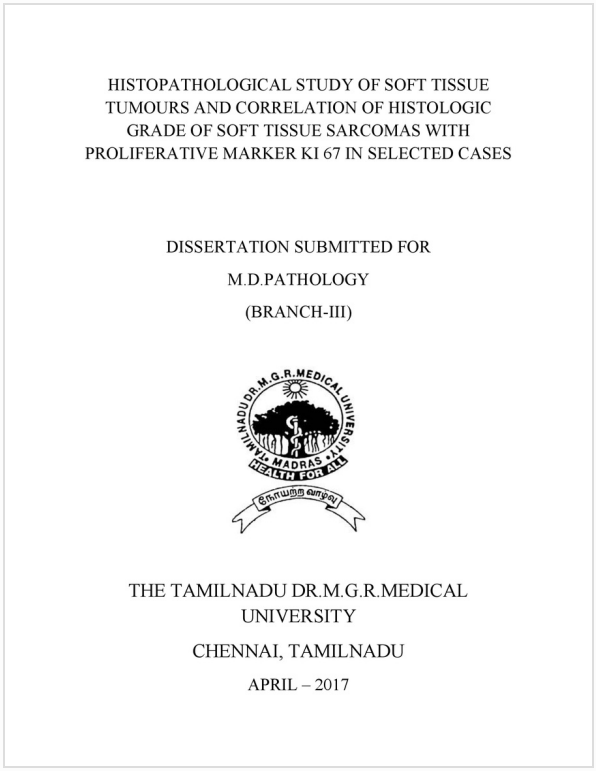

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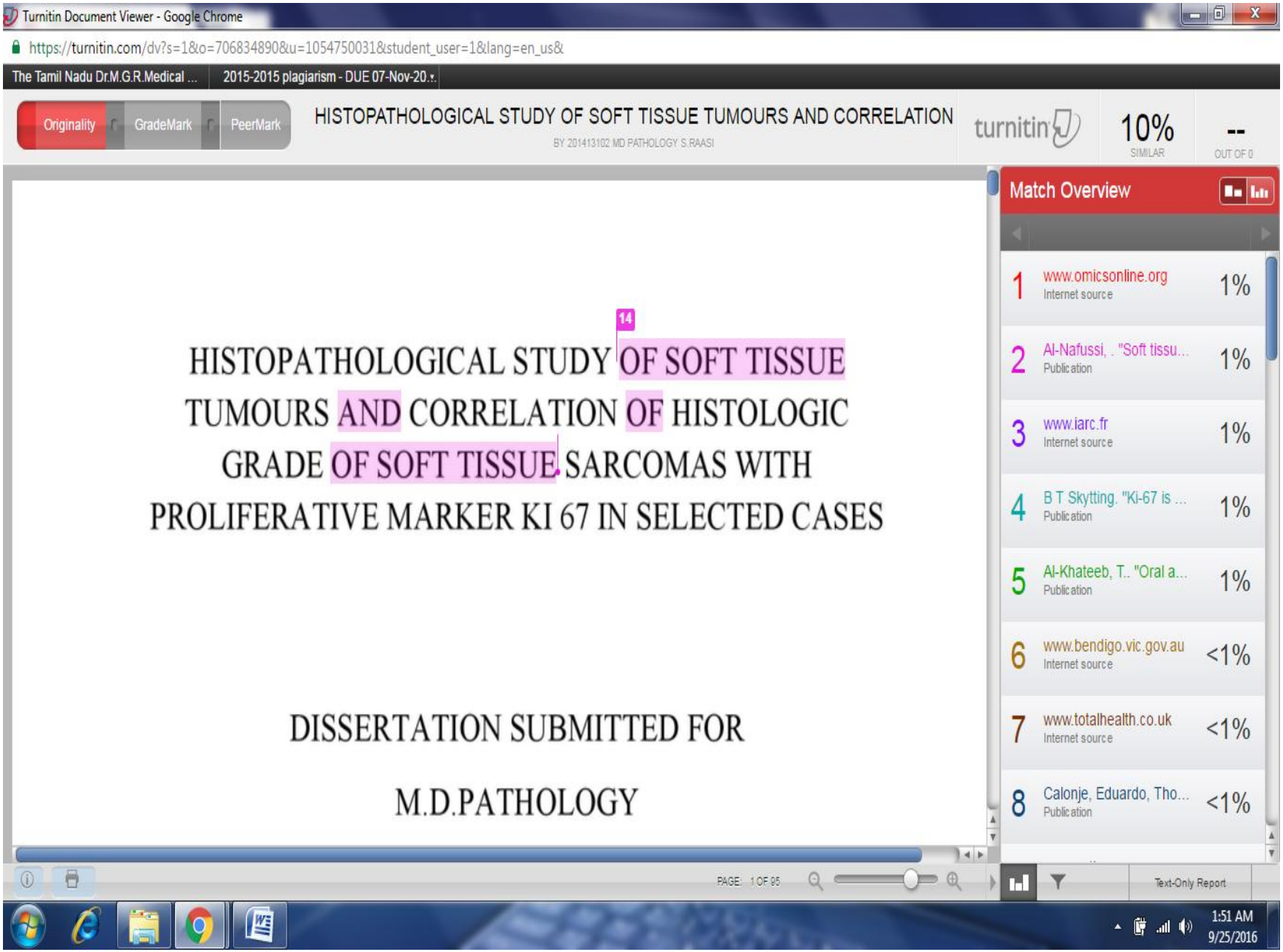
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