

Original Article

An Audit of the Diagnosis and Reporting of Soft Tissue Sarcomas at the Lagos University Teaching Hospital

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ABSTRACT

Background: The effective management of patients with cancer is predicated on the right diagnoses and other relevant parameters included in the pathology report. This is particularly important in soft tissue pathology where arriving at the right diagnosis is often challenging. The aim of this study, therefore, was to perform an audit of sarcoma diagnosis and reporting in our institution. **Methods:** Slides of soft tissue sarcomas diagnosed in our institution over a 5-year period were reviewed with specialist soft tissue pathologists. Ancillary immunohistochemistry and fluorescent *in situ* hybridization were performed where necessary. The contents of the reports were assessed using a diagnostic checklist developed by the Association of Directors of Anatomic and Surgical Pathology. **Results:** Fifty-five of the 62 patients studied (88.7%) were correctly identified as sarcomas. However, the correct diagnoses were made in only 27 patients (43.6%). Kaposi sarcoma and dermatofibrosarcoma protuberans were the most recognized sarcomas, while leiomyosarcoma, myxofibrosarcoma, and malignant peripheral nerve sheath tumor were the least recognized sarcomas. The most reported parameters included the histologic type (100%) and size (89.7%), while the percentage of necrosis (0%) and the stage (0%) were the least reported parameters. **Conclusion:** A pattern based approach is important for the accurate diagnosis of soft tissue sarcomas. Some essential prognostic parameters and information needed for management were not included in the histopathology reports. The adoption of a structured reporting format and multidisciplinary team meetings will help to ensure the inclusion of such important information in the pathology report.

KEYWORDS: *Audit, LUTH, soft tissue sarcomas*

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INTRODUCTION

The diagnosis of soft tissue sarcomas can be challenging for the practicing general pathologist. The rarity of these tumors, their varying histological appearances, and the multitudes of subgroups of classification all contribute to the diagnostic difficulty of these tumors on routine hematoxylin and eosin (H and E) stained sections.^[1,2] This is further compounded by the fact that sarcomas can just as easily have an epithelioid or round cell morphology thus mimicking carcinomas, melanomas, and lymphomas, as they can be imitated by the sarcomatous variants of these tumors.^[3,4] Some sarcomas such as low grade fibromyxoid sarcoma, epithelioid sarcoma, and

epithelioid hemangioendothelioma have deceptively bland cytology further complicating matters.^[5] In fact, the misinterpretation of the morphology of these lesions is a major cause of misdiagnosis by the practicing general pathologist.^[6]


Although the use of immunohistochemical techniques has improved the diagnostic accuracy of soft tissue sarcomas, there remains nevertheless a challenge even at

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this level of testing. In one report, misdiagnosis that was related to the use of immunohistochemistry was majorly because of wrong interpretation of the pattern of staining rather than the unavailability of crucial uncommon stains or the request of wrong panels of immunostains.^[6] Therefore, it was noted that some of these discrepancies could be minimized by paying attention to the pattern of staining i.e., nuclear, paranuclear, or cytoplasmic, as well as by being careful not to interpret background staining.^[6] Ancillary cytogenetic and molecular studies are commonly employed in the diagnosis of certain soft tissue sarcomas and have been shown to improve diagnostic accuracy.^[7] Centers, such as those in low to middle income countries, where such tests are largely unavailable often have diagnostic challenges in this regard, and therefore, run the risk of misdiagnosis.^[6]

In addition to making the right diagnosis, certain information are important for prognostication and treatment, and therefore, must be recorded in the histopathology report. These include size, grade, tissue plane or depth, relation to the margins, and stage. The grade, stage, and depth of the tumor are important for prognostication. The grade is also useful for planning treatment, and with the size and depth is also important for staging. The relation of the tumor to the margin is predictive of local recurrence.^[8-10]

An inadequate report especially one with the wrong diagnosis has significant implications for management. In one study, approximately 70% of patients with sarcomas receive inappropriate medical treatment because of the wrong diagnosis.^[11] Reviews, such as this, are one of the tools that can help to improve diagnostic accuracy. The aim of this study was therefore to conduct an audit of diagnosis and reporting of soft tissue sarcomas seen in our institution over a 5-year period.

METHODS

Archival H and E stained slides containing formalin-fixed paraffin embedded tissue sections of patients of soft tissue sarcomas diagnosed from January 2012 to December 2016 were retrieved and reviewed with the team of specialist soft tissue pathologists at the Royal National Orthopedic Hospital, UK. Where definitive diagnosis could not be reached on H and E, immunohistochemistry and fluorescent *in situ* hybridization (FISH) were performed.

Immunohistochemistry was performed on representative blocks using the Leica Bond 3 fully automated immunohistochemistry staining system. The choice of panels used for each individual case depended on the morphology of the tumor and the differential diagnoses entertained. These included SMA, S100, desmin,

myogenin, caldesmon, MNF116, EMA, CD45, TdT, MUC4, STAT6, HMB45, vimentin, INI1, CD99, CD31, CD117, and synaptophysin. Appropriate positive controls were used for each of the individual stains.

FISH was performed using probes for MDM2 (Abbott Molecular, USA), EWSR1 (Abbott Molecular, USA), TFE3 (Zytovision, Germany), and SS18 (Abbott Molecular, USA) for sections suspected to be well differentiated liposarcoma, Ewing sarcoma, alveolar soft part sarcoma, and synovial sarcoma, respectively. For these sections, deparaffinised sections were pretreated with deionized water in a pressure cooker for 5 min and digested with pepsin at 37°C for 50 min. Subsequently, the tissue sections and appropriate FISH probes as listed above were co-denatured at 72°C for 10 min and hybridized overnight at 45°C, after which washing was performed. Slides were then counterstained with 4, 6-diamidino-2-phenylindole and mounted with coverslips. At least 50 non-overlapping nuclei were assessed for the relevant cytogenetic changes using a fluorescence microscope (Olympus BX61, Japan) that was equipped with appropriate filters, a charge-coupled device camera (Olympus XM10), and the FISH imaging and capturing software Cell Imaging system (Olympus Soft Imaging Solution, Germany).

File copies of the histology reports of the patients were retrieved and assessed for the inclusion of important parameters according to the recommendation of the Association of Directors of Anatomical and Surgical Pathology (ADASP).^[12] These included size, depth, histologic diagnoses, grade, presence or absence of necrosis, percentage of necrosis if present, status of the margins, and stage. Patients who underwent core needle and incisional biopsies were excluded from this aspect of the study. These data were classified and analyzed using the SPSS 22 statistical package, and represented in tables, charts, and graphs. Ethical approval was obtained from the institutions Health and Research Ethics Committee.

RESULTS

Sixty-two patient's samples were seen during the study period. None of these diagnoses were made using immunohistochemistry or other ancillary tests. The median age of the patients was 36 years, the age range was 3 months to 79 years, and the peak age group was the 30 years [Figure 1].

The most common sarcoma Initial diagnoses were Kaposi sarcoma (KS) (25.8%), malignant mesenchymal tumor (24.2%), and dermatofibrosarcoma protuberans (DFSP) (16.1%). Figure 2 shows the histologic spectrum of these initial diagnoses.

After review by the team of soft tissue specialists, 55 of the 62 patients (88.7%) were found to have been correctly recognized as soft tissue sarcomas. Three however turned out to be benign and 4 to be non-mesenchymal malignancies.

In 27 of the specimens (43.6%) the specific diagnoses were made correctly. These were predominantly KS and DFSP [Table 1]. All 16 patients of KS were correctly diagnosed; however 2 benign vascular tumors were overdiagnosed as KS. All 7 patients with DFSP were also correctly diagnosed; however, a case of fibrosarcomatous DFSP and another of undifferentiated pleomorphic sarcoma were under-diagnosed as DFSP [Table 2].

All 3 patients each of leiomyosarcoma and myxofibrosarcoma were incorrectly diagnosed and they never featured in any of the differential diagnoses. Malignant peripheral nerve sheath tumor (MPNST) featured the most among the differential diagnoses of spindle cell sarcomas, however the single patient with a final diagnosis of MPNST was not recognized [Table 3].

Of the round cell sarcomas, embryonal rhabdomyosarcoma was correctly diagnosed in 60%

of patients. The remaining were undifferentiated round cell sarcomas, a diagnosis that can only be made after judicious use of ancillary studies.

The file copies of 39 reports were retrieved for assessment of inclusion of important parameters according to the ADASP guidelines. These included 26 resections and 13 punch biopsies. Only resection specimens were assessed for stage. Samples received piecemeal, and could therefore not be assessed for margin status, were excluded. DFSP is by definition a grade 1 tumor, while embryonal rhabdomyosarcoma (except spindle cell and botryoid variants), angiosarcoma, and soft tissue osteosarcoma are grade 3 tumors by definition.⁸ These tumors were not assessed for their grade. The stage and percentage of necrosis were the least reported parameters (0% each), while the diagnosis and the size were the most reported parameters (100% and 53.8%, respectively) [Table 4].

Table 1: Patients with concordant diagnosis

Diagnosis	Number of patients (%)
Kaposi sarcoma	16 (25.8)
Embryonal rhabdomyosarcoma	3 (4.8)
DFSP	7 (11.3)
Angiosarcoma	1 (1.6)
Total	27 (43.6)

DFSP=Dermatofibrosarcoma protuberans

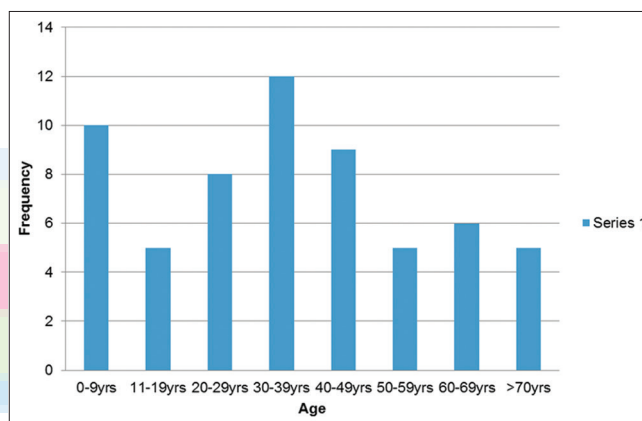


Figure 1: Age distribution of soft tissue sarcoma patients diagnosed in LUTH between January 2012 and December 2016

Table 2: Cases with discrepant diagnoses

Previous diagnosis	Final diagnosis	Number of patients (%)
Benign-malignant discrepancy		
Kaposi sarcoma	Spindle cell hemangioma	1 (1.6)
Kaposi sarcoma	Capillary hemangioma	1 (1.6)
Malignant mesenchymal tumor	Intramuscular myxoma	1 (1.6)
Malignant-malignant discrepancy		
Embryonal rhabdomyosarcoma	Undifferentiated round cell sarcoma	3 (4.8)
Alveolar rhabdomyosarcoma	Undifferentiated epithelioid sarcoma	1 (1.6)
Angiosarcoma	Low grade spindle cell sarcoma	1 (1.6)
Liposarcoma	Myxofibrosarcoma	1 (1.6)
DFSP	Undifferentiated pleomorphic sarcoma	2 (3.2)
Fibrosarcoma	Undifferentiated pleomorphic sarcoma	1 (1.6)
Pleomorphic rhabdomyosarcoma	Pleomorphic leiomyosarcoma	1 (1.6)
DFSP	Fibrosarcomatous DFSP	1 (1.6)
Mesenchymal - non-mesenchymal discrepancy		
Malignant mesenchymal tumor	Lymphoma	3 (4.8)
Malignant mesenchymal tumor	Carcinoma	1 (1.6)
Total		18 (29.0)

DFSP=Dermatofibrosarcoma protuberans

Table 3: Cases with broad diagnoses and their final diagnoses

Previous diagnosis	Final diagnosis	Number of patients (%)
Malignant mesenchymal Tumor with differential of rhabdomyosarcoma	Undifferentiated round cell sarcoma	1 (1.6)
Differentials of anaplastic nephroblastoma, Ewing sarcoma provided	Clear cell sarcoma of the kidney	1 (1.6)
Small round blue cell tumor with differentials of olfactory neuroblastoma, Ewing sarcoma, Embryonal rhabdomyosarcoma	Embryonalrhabdomyosarcoma	1 (1.6)
Malignant mesenchymal tumor	Solitary fibrous tumor	1 (1.6)
Malignant spindle cell sarcoma	Myxofibrosarcoma	1 (1.6)
Malignant mesenchymal tumor	MPNST (triton tumor)	1 (1.6)
Malignant mesenchymal tumor	Embryonalrhabdomyosarcoma	1 (1.6)
Pleomorphic sarcoma	Pleomorphic leiomyosarcoma	2 (3.2)
Malignant mesenchymal tumor with differential of MPNST	Myxofibrosarcoma	1 (1.6)
Round cell sarcoma	Undifferentiated round cell sarcoma	1 (1.6)
Malignant mesenchymal tumor	Low grade spindle cell sarcoma	1 (1.6)
Malignant mesenchymal tumor with differentials of undifferentiated pleomorphic sarcoma, MPNST and pleomorphic rhabdomyosarcoma	Undifferentiated pleomorphic sarcoma	1 (1.6)
Pleomorphic sarcoma	Undifferentiated pleomorphic sarcoma	1 (1.6)
Pleomorphic sarcoma	Myxofibrosarcoma	1 (1.6)
Malignant mesenchymal tumor	Extra skeletal osteosarcoma	1 (1.6)
Malignant mesenchymal tumor	Malignant mixed mullerian tumor	1 (1.6)
Total		17 (27.4)

MPNST=Malignant peripheral nerve sheath tumor

Table 4: Documentation of important parameters in the histology report

Parameter	Reported (%)	Not reported (%)	Total
Size	35 (89.7)	4 (10.3)	39
Diagnosis	39 (100)	0 (0)	39
Plane	21 (53.8)	18 (46.2)	39
Grade	2 (6.9)	27 (93.1)	29
Presence of necrosis	7 (17.9)	32 (82.1)	39
Percentage necrosis	0 (100)	39 (100)	39
Margins	10 (47.6)	11 (52.4)	21
Stage	0 (0)	26 (100)	26

DISCUSSION

Although the study shows that the majority of sarcomas were correctly recognized as malignant, a significant number were diagnosed using the broad term “malignant mesenchymal tumor.” Using the traditional features of malignancy that include hyperchromasia, pleomorphism, mitoses, and necrosis therefore helps in the recognition of most soft tissue sarcomas as malignant neoplasms. These traditional cytologic features, however, should have been helpful in identifying the intramuscular myxoma misdiagnosed in this study as malignant, as intramuscular myxomas, even when cellular, rarely show mitoses, pleomorphism, hyperchromasia, or necrosis.^[13] None of the sarcomas with deceptively bland cytologic features were seen in the study. The rarity of these tumors

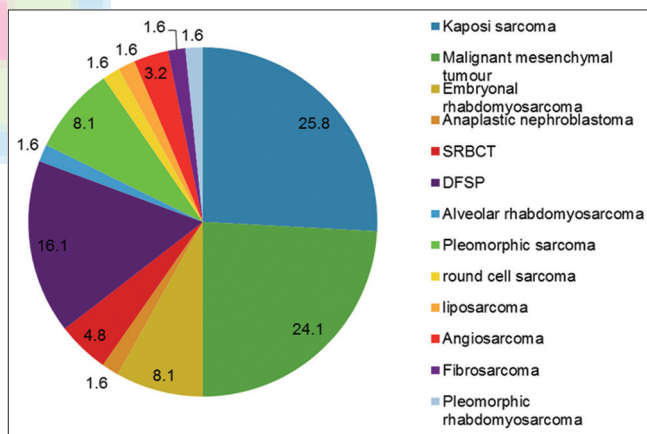


Figure 2: Histologic spectrum of initial diagnosis of soft tissue sarcomas

is therefore of reasonable benefit to the pathologist who pays attention to the cytology of the tumor cells when proffering a diagnosis. Although malignancy was correctly recognized in most of the patient’s specimens, the right diagnosis was often not considered in the differential diagnoses, especially in those tumors with pleomorphic and spindle cell morphology. This suggests that the architectural pattern was not given as much attention as the cytology of the tumor cells when the list of differentials was drawn. After ruling out a reactive process for any given lesion, the low power

architectural pattern, the cytology of the tumor cells, and the characteristics of the stroma are of great value in formulating decent differential diagnoses.^[14] A broad knowledge of the various soft tissue sarcomas and their architectural patterns therefore lends itself greatly when drawing up differential diagnoses.

KS and DFSP were the most commonly recognized tumors. Being the most common lesions seen in the institution of study, one can infer that the more familiar a lesion is to the pathologist, the greater the chance is of making the right diagnosis. External quality assurance programs, audits, and educational workshops are educational tools that help the pathologist recognize rarer lesions.^[15] Although KS was well recognized, one must always bear in mind that the patch stage of KS can be subtle and can often be overlooked or misdiagnosed as a benign lesion. In the absence of immunohistochemistry for Human herpes virus 8, a suspicion can be raised in the histology report especially in the right clinical context. The spindled areas of spindle cell hemangioma are often reminiscent of KS and can be misdiagnosed as such (as was the case in this study). However, the presence of cavernous areas and epithelioid cells with intracytoplasmic lumina containing red blood cells in addition to the spindle cell areas should assure one of the right diagnosis.^[14] The storiform pattern of DFSP was also well recognized though the case of fibrosarcomatous DFSP was missed. Attention should therefore be paid to the presence of mitotically active fascicular areas within an otherwise storiform tumor characteristic of DFSP as this signifies progression to a higher grade and more aggressive malignant neoplasm.^[16]

Myxofibrosarcoma, leiomyosarcoma, and MPNST were the least recognized tumors in this study. The first two because they never featured in any of the differential diagnoses, while the last because it featured the most in the differentials yet was not recognized when it was the right diagnosis. Myxofibrosarcomas are relatively common tumors. They occur most commonly in the superficial limbs of the elderly. Although they show a broad spectrum of cellularity, mitoses, and pleomorphism, they most often have a multinodular growth pattern with incomplete septa compartmentalizing the myxoid stroma. Prominent elongated curvilinear thin walled vessels are characteristic. Cellular atypia is often obvious in contrast to low grade fibromyxoid sarcoma.^[13] Myxoid liposarcoma is a histologic differential of myxofibrosarcoma. It is therefore not surprising that a case of myxofibrosarcoma was misdiagnosed as such. However, myxoid liposarcoma has a more uniform population of spindle cells and a delicate plexiform vasculature. Lipoblasts are

often present, while frank cytologic atypia is usually not seen. Pleomorphic leiomyosarcomas often have lower grade fasciculated areas composed of cells with blunt ended nuclei, perinuclear vacuoles, and eosinophilic cytoplasm in addition to malignant fibrous histiocytoma-like areas.^[17] This is in contrast to the much rarer pleomorphic rhabdomyosarcoma that more often has a sheet like architectural pattern rather than a fasciculated architecture. Immunohistochemistry further helps to differentiate these entities.^[14] When making a diagnosis of MPNST preference must be given to a tumor arising from a peripheral nerve or a benign nerve sheath tumor. In the absence of these, schwann cells differentiation must be seen, evidenced by alternating hyper- and hypodense areas composed of cells with wavy, buckled, or comma shaped nuclei. If the tumor appears fibrosarcomatous, then there must be immunohistochemical or ultra structural evidence of schwann cell differentiation before a diagnosis of is made.^[14,17] Perivascular tumor condensation and tumoral herniation into vascular lumina are additional helpful features of MPNST.^[18]

It is pertinent to note that a diagnosis of fibrosarcoma should only be entertained after other diagnoses have been ruled out by immunohistochemistry or other ancillary tests. These differentials include monomorphic fibrous synovial sarcoma, MPNST, desmoplastic leiomyosarcoma, clear cell sarcoma, sarcomatoid mesothelioma, spindle cell rhabdomyosarcoma, and spindle cell carcinomas.^[9] It is also noteworthy that by convention, high grade fibroblastic sarcomas with no demonstrable evidence of differentiation are designated undifferentiated pleomorphic sarcoma (UPS) rather than high grade fibrosarcoma as was reported in this study.^[14] In the same light, UPS often shows bizarre looking anaplastic cells with intense cytoplasmic eosinophilia that could suggest myoblastic differentiation.^[13] In fact, pleomorphic rhabdomyosarcomas were once reclassified as the so called "malignant fibrous histiocytoma."^[14] It is advisable that a diagnosis of pleomorphic rhabdomyosarcoma should be confirmed with ancillary studies, and it is worth noting that they are very rare tumors. Therefore, a pleomorphic sarcoma with eccentric nuclei and abundant eosinophilic cytoplasm is more likely to be UPS or most other types of pleomorphic sarcoma than pleomorphic rhabdomyosarcoma. One must also remember that UPS is a diagnosis of exclusion.

Carcinomas, lymphomas, and melanomas can have a sarcomatoid appearance and vice versa.^[17] In fact, it can be extremely difficult to differentiate UPS from sarcomatoid carcinoma. It is generally assumed

that a pleomorphic malignant neoplasm arising in the skin, mucosal surface, or parenchymal organ is a sarcomatoid carcinoma, until proven otherwise. This is useful as sarcomatoid carcinomas do not always retain immunohistochemical markers of epithelial differentiation, while UPS can show focal immunopositivity for epithelial markers.^[17] Staining for p63, however, has been shown to be useful in this setting as only about 9% of sarcomas are positive for this stain.^[19] Childhood lymphomas occur more commonly than embryonal rhabdomyosarcomas. A diagnosis of a lymphoma should always be entertained especially when there is no obvious rhabdomyoblastic differentiation. Although ancillary testing is required to confirm a diagnosis of lymphoma, it should nevertheless feature in the differential diagnosis of childhood small round blue cell tumors.^[19,20]

Some essential histologic parameters were absent from the reports. The grade, stage, presence and percentage of necrosis were the least reported. It is important to note that these parameters are useful for planning treatment and prognostication. Multidisciplinary team meetings (MDTs) and the adoption of reporting proformas help to ensure that these key data are included in the report. An increase in the completeness of histopathology reporting has been noted with the introduction of reporting proformas and institutions where checklists are used demonstrate higher rate of complete histology reports.^[21,22] In one study MDTs and discussions were shown to encourage pathologists to improve their reports to fulfill guidelines and to provide important histological information that were necessary for planning treatment.^[23]

CONCLUSION

Although sarcoma diagnosis can be challenging for the general pathologist, a wide knowledge of the morphology and behavior of the many entities and a pattern based approach is vital for making the right diagnosis or at least considering it in the differential diagnoses. Audits, workshops, and external quality assurance are beneficial in this regard. We also recommend the adoption of structured reporting and MDTs for improving the quality of sarcomas reports to ensure proper treatment planning and prognostication.

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Conflicts of interest

There are no conflicts of interest.

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