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DISTRIBUTION AND EVALUATION OF MUSCULOSKELETAL SOFT TISSUE TUMORS IN HISTOPATHOLOGICAL SPECIMENS

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ABSTRACT

Background: Soft tissue sarcomas, in contrast to benign lesions, are rare and account for 1% of all malignant tumors. According to the World Health Organization (WHO), soft tissue tumors are classified based on their resemblance to their normal counterpart. Regardless that tumors-histopathological study is the confirmatory test, certain tumors require immunohistochemical staining and genetic analysis to categorize them. **Methods:** A part of a retrospective, single-center study, all the histopathological reports of musculoskeletal soft tissue tumors in the period of January 2017 - December 2019, were collected from Princess Iman Research Center (PIRC) at King Hussein Medical City (KHMC) in Jordan. Tumors were assessed according to their origin and analyzed according to the anatomical locations as well as to the age groups and genders. **Results:** In a sample of 350 histopathological specimens, 54.3% were males and 45.7% were females. The mean age for the patients was 45.12 (±16.51) years. Soft tissue sarcomas represent 9.4 % of the findings. Lipoma was the most common benign tumor (65.4 %), followed by giant cell tumors of tendon sheath (16%) and glomus tumor (3.4%) respectively. Regarding soft tissue sarcoma, Liposarcoma was the most common (2.6%), followed by synovial sarcoma (2.3%) and Leiomyosarcoma (1.7%). The back was the most common location of tumors (28.3%), while hand, thigh and shoulder had the following frequency: 16 %, 14.3 %, and 10.3 % respectively. **Conclusion:** Musculoskeletal soft tissue tumors studies are limited and their frequency is difficult to estimate. Understanding their histopathological types and their distribution regarding age, gender and anatomical locations would aid in diagnosis. Increasing age, a tumor arising from muscles; small round cells, and those of unknown origin, in addition to tumors arising in the leg; pelvis; spine and thigh are more predicted for malignant soft tissue tumors.

KEYWORDS: Musculoskeletal soft tissue tumors, Benign, Malignant, Jordan.

INTRODUCTION

Soft tissue tumors are neoplasms that arise from supporting and connective tissues of the body, this includes muscles, fibrous tissues, fats, nerves and vessels.[1] In contrast to benign lesions, malignant soft tissue sarcomas are rare and account for 1% of all malignant tumors. This equals three to four times the prevalence of bone sarcomas.[2,3]

In the same manner as bone tumors classification, soft tissue neoplasms are classified based on their resemblance to their normal counterpart. World Health Organization (WHO) classification which was published in 2013; categorized soft tissue tumors into Adipocytic tumors, Fibroblastic or myofibroblastic tumors, Fibrohistiocytic tumors, Smooth-muscle tumors, Skeletal-muscle tumors, Nerve sheath tumors, Tumors of uncertain differentiation and Undifferentiated or unclassified sarcomas.[4,5]

Regardless that most tumors are diagnosed histopathologically, some tumors are poorly differentiated and required immunohistochemical staining and genetic analysis to categorize them.[6] Synovial sarcoma for example does not have a normal cell counterpart. It arises near joints but not from the synovium nor the contents of the joints. Therefore, the name of synovial sarcoma is a misnomer.[7]

In Jordan, there is limited data regarding soft tissue tumors epidemiology and distribution. Therefore, the objective of this study is to review the histopathological types of soft tissue neoplasms and their distribution regarding age, gender and anatomical locations. This would help in better understanding of soft tissue tumors and aid in diagnosis.

MATERIALS AND METHODS

In this retrospective, single-center study; the histopathological reports of musculoskeletal soft tissue tumors were collected from Princess Iman Research Center (PIRC) at King Hussein Medical City (KHMC), which is a tertiary military hospital and one of the limited oncology-laboratory centers in Jordan. PIRC's records and patients' electronic system were utilized to gather all diagnostic and excisional biopsies results in the period of January 2017 - December 2019. The study was approved by the local ethical committee of the Royal Medical Services of Jordan.

The anatomical locations of the tumors and the histopathological findings were abstracted from the patients' reports, in addition to patients' ages and genders. Soft tissue tumors were classified into benign and malignant tumors. Additionally, tumors were assessed according to their origin and analyzed according to their anatomical locations as well as to the age groups and genders.

Three hundred and fifty biopsies were included. Inclusion criteria add histopathological results of musculoskeletal soft tissue tumors of limbs and trunk, in addition to reports with a single diagnosis. Visceral and head soft tissue tumors, musculoskeletal bone tumors and reports with more than one possible diagnosis were excluded.

Statistical Data Analysis

Descriptive analysis with the mean and standard deviation was applied to continuously measured variables, and with the frequency and percentages for categorical variables. The statistical normality assumption was tested with the histograms and the statistical Kolmogrove-Smirnov test and the equal variance assumption was tested with Levene's test.

The Unpaired samples t-test was used to assess the statistical significance of mean difference on metric variables across patients' binary dichotomous variables levels, and the chi-squared test of independence (χ2-test) was used to assess the statistical significance of associations between categorically measured variables. However, the residual analysis with the adjusted standardized residuals was used along with the chi-squared test of association to identify influential cells within the contingency tables for their clinical implications. Cells within the contingency (chi-squared) test tables that had a standardized adjusted residual above or below (+ 1.96) was considered as an influential cell with a more or less predicted likelihood for the analyzed outcomes like malignancy and association with patients ages and genders.

The chi-squared Goodness-Of-Fit test (χ2- G.O.F) was used to assess the statistical significance of the distribution of soft tissue tumors across the patients' body locations and age groups.

The SPSS IBM V21 was used for the statistical data analysis and the alpha significance level was considered at the 0.050 level.

RESULTS

Three hundred and fifty soft tissue tumor-biopsies were reviewed retrospectively. Table-1 demonstrates the patients' sociodemographic characteristics. Of all patients, 190 (54.3%) were males and 160 (45.7%) were females. The mean age for the patients was equal to 45.12 (±16.51) years.

Regarding age groups; 6.9% of them were aged twenty years or below; 11.4% of them were aged between 21-30 years; 22.3% were aged between 31-40 years; 24.1% were aged between 41-50, however, 14.9% of them were aged between 51-60 years and the remainder 19.4% of the patients were aged ≥ 61 years.

Table-1: Patients sociodemographic characteristics N=350

	Frequency	Percentage
Sex		
Female	160	45.7
Male	190	54.3
Age (years)-Mean (SD)		45.12 (16.51)
Age group		
≤ 20 years	24	6.9
21-30 years	40	11.4
31-40 years	78	22.3
41-50 years	88	25.1
51-60 years	52	14.9
≥ 61 years	68	19.4

The table-2 Displays the yielded findings from analyzing the patients' soft tissue tumor characteristics, the distribution of the soft tissue tumors across the patients' body parts were distributed as follows: the majority (28.3%) of tumors were in the back region; followed by hand 16%; thigh tumors account for 14.3%; 10.3% of the patients had shoulder tumors; 7.1% in the elbow and forearm location; ankle and foot region as well as chest wall had the same percentage 4.3%; similarly, arm and knee had the same frequency 3.7%; leg tumors and spine had the following percentage respectively 3.4%; 1.4%. Out of the 350 patients, 33 patients (9.4%) were found to have malignant soft tissue tumors and the remaining majority of the patients 90.6% had benign soft tissue tumors.

Table-2: Patients' histopathological identified soft tissue tumor types and their clinical characteristics.		
	Frequency	**Percentage**
Anatomic body location of the tumor		
Ankle and foot	15	4.3
Arm	13	3.7
Back	99	28.3
Chest Wall	15	4.3
Elbow and forearm	25	7.1
Hand	56	16
Knee	13	3.7
Leg	12	3.4
Pelvis	11	3.1
Shoulder	36	10.3
Spine	5	1.4
Thigh	50	14.3
Tumor general classification		
Benign	317	90.6
Malignant	33	9.4

With regards to the origin of the soft tissue tumors, note table-3, 66.3% of the histopathological finding were fat producing tumors, another 16% of patients' tumors were of synovial origins, 4% of them originated from fibrous producing tissue, and 3.4% originated from glomus body, 2.9% were tumor-like tissue origins, 2.6% of unknown origin, 2.3% from muscular tissue, another 2% from small round blue cells and 0.3% from Neural crest and Primitive mesenchymal cells respectively.

Tumor like pathologies is a category, where the tumor did not originate from one cell as in the case of true neoplasm. However, they share the clinical and radiological features with it. In our sample, there were 4 cases of synovial lipomatosis; 3 cases of myositis ossificans, one case of pigmented villonodular synovitis and one case of hamartoma.

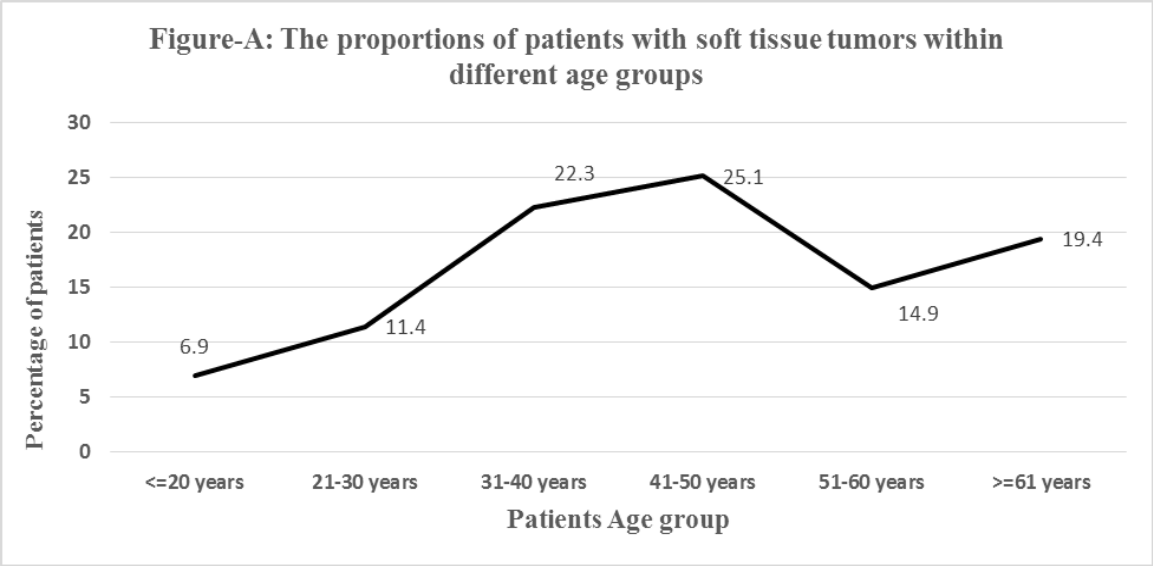
Lipoma was the most commonly diagnosed benign tumor in our study and accounts for 65.4% of histopathological findings; followed by Giant cell tumor of tendon sheath (16%); glomus tumor was diagnosed in 3.4%; tumor-like pathology and desmoid tumor share the same frequency of 2.9%. Regarding malignant tumors, liposarcoma was the most commonly diagnosed (2.6%), followed by leiomyosarcoma (1.7%); lymphoma accounts for 1.1% and 0.9% for plasmacytoma. Clear cell sarcoma and Pleomorphic sarcoma were diagnosed in less than 1%.

Table-3: Patients histopathological identified soft tissue tumor types and their clinical characteristics.		
Tumor origin general types		
Fat Producing	232	66.3
Synovial origin	56	16
Fibrous Producing	14	4
Glomus body	12	3.4
Tumor like origins	10	2.9
Unknown Origin	9	2.6
Muscle Origin	8	2.3
Small Round Blue Cell	7	2
Neural crest	1	0.3
Primitive mesenchymal cells	1	0.3
Histopathological Returned tissue finding		
Lipoma	229	65.4
Giant cell tumor of the tendon sheath	56	16
Glomus tumor	12	3.4
Tumor Like	10	2.9
Desmoid tumor	10	2.9
Liposarcoma	9	2.6
Synovial sarcoma	8	2.3
Leiomyosarcoma	6	1.7
Lymphoma	4	1.1
Plasmacytoma	3	0.9
Clear cell sarcoma	1	0.3
Myxoma	1	0.3
Pleomorphic sarcoma	1	0.3

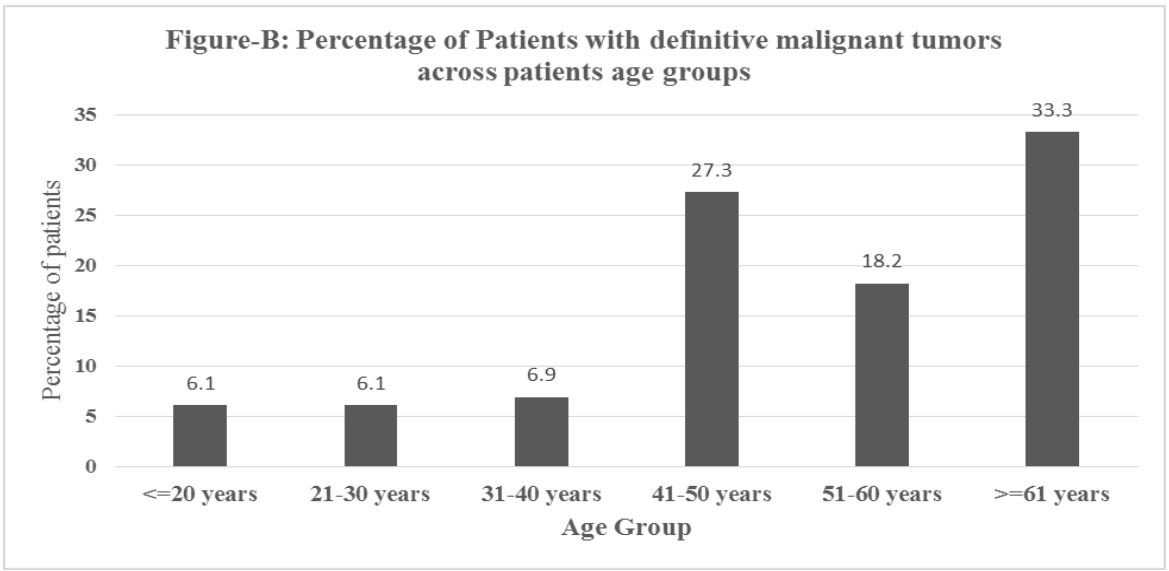
DISCUSSIONS

It is difficult to estimate the annual incidence and the prevalence of soft tissue tumors, because many cases are asymptomatic, in addition to the fact that not all cases need a radiological nor histopathological diagnosis. Understanding the distribution of soft tissue tumors and their histopathological subtypes aid in diagnosis. In Jordan, no sufficient resources are illustrating the distribution of soft tissue tumors. Most of the local studies are hospital-based or concerning certain ages, categories, or histopathological types. Regional resources are limited as well and usually assess bone and soft tissue tumors together.

In this study, we review the histopathological findings of three hundred and fifty soft tissue tumor-specimens in a tertiary hospital. By considering the distribution of the patients with soft tissue tumors across the defined age groups, note figure-A, people aged between 31-40 and those aged between 42-50 years as well as those aged ≥ 61 years, were found to be significantly more predicted than expected to have soft tissue tumor than people within the other remaining age groups, p<0.001.



According to our sample, there were no sex differences regarding soft tissue tumors distribution (p=0.690). Conversely, patients diagnosed with a malignant tumor were significantly older (Mean=52.72 years) than those who had benign soft-tissue tumors (Mean = 44.37), p=0.009, table-4. Patients older than 41 years, were significantly more predicted for malignant soft-tissue tumors than those younger than 40 years, p=0.017, see Figure-B. Additionally, the patients' soft-tissue tumor location had converged significantly on their malignancy risk, p<0.001. The patients with leg, pelvis, spine and thigh soft tissue tumors were found to be significantly more predicted for malignancy than the other patients with soft-tissue tumors found in other body sites.



Moreover, the analysis showed that the patients' soft-tissue origins had converged significantly on their risk of having malignant soft-tissue tumors, those patients with tumors originating from muscles, small round cells and those of unknown origins were significantly more likely to be malignant, p<0.001.

Table-4: Bivariate analysis of the patients' soft tissue malignancy.

	Tumor classification		Test statistic	p-value
	Benign	**Malignant**		
Sex				
Female	146 (46.1)	14 (42.4)	$\chi2(1)=0.14$	0.69
Male	171 (53.9)	19 (57.6)		
Age (years) mean (SD)	44.37 (16.33)	52.27 (16.72)	t(348)=2.64	0.009
Age Group				
≤ 20 years	22 (6.9)	2 (6.1)	$\chi2(5)=8.10$	0.152
21-30 years	38 (12)	2 (6.1)		
31-40 years	75 (23.7)	3 (9.1)		
41-50 years	79 (24.9)	9 (27.3)		
51-60 years	46 (14.5)	6 (18.2)		
≥ 61 years	57 (18)	11 (33.3)		
Age group collapsed based on 40 year				
≤ 40 years	135 (42.6)	7 (21.2)	$\chi2(1)=5.66$	0.017
≥ 41 years	182 (57.4)	26 (78.8)		
Tumor location				
Ankle and foot	12 (3.8)	3 (9.1)	$\chi2(11)=82.43$	<0.001
Arm	11 (3.5)	2 (6.1)		
Back	98 (30.9)	1 (3)		
Chest Wall	15 (4.7)	0		
Elbow and forearm	24 (7.6)	1 (3)		
Hand	56 (17.7)	0		
Knee	12 (3.8)	1 (3)		
Leg	7 (2.2)	5 (15.2)		
Pelvis	7 (2.2)	4 (12.1)		
Shoulder	36 (11.4)	0		
Spine	0	5 (15.2)		
Thigh	39 (12.3)	11 (33.3)		
Tumor origins				
Fat Producing	225 (71)	7 (21.2)	$\chi2(11) =149.34$	<0.001
Fibrous Producing	14 (4.4)	0		
Glomus body	12 (3.8)	0		
Muscle Origin	0	8 (24.2)		
Neural crest	0	1 (3)		
Primitive mesenchymal cells	1 (0.3)	0		
Small Round Blue Cell	0	7 (21.2)		
Synovial origin	56 (17.7)	0		
Tumor like origins	9 (2.8)	1 (3)		
Unknown Origin	0	9 (27.3)		

By comparing patients' genders on their measured soft-tissue tumors, table-5, the yielded analysis findings showed that the male and female patients in the sample did not differ significantly for their age and location of the tumors they had. However, the analysis showed that male and female patients differed significantly concerning their soft-tissue tumor origins, the male patients were significantly more predicted for fat producing soft-tissue tumors than did females. Conversely, females were significantly more predicted for fibrous and synovial tumor origins than did males, p=0.011. Another analysis suggested that females were significantly more predicted for final diagnosis with desmoid and giant cell tumors but less predicted for lipomas than did male patients, p=0.033.

Table-5: Bivariate analysis of the patients' gender for statistically significant differences in soft tissue tumors findings.

	Patients sex		Test statistic	p-value
	Female	**Male**		
Age (years) mean (SD)	44.54 (16.84)	45.61 (16.24)	t(348)=0.60	0.547
Age group collapsed based on 40 year				
≤ 40 years	62 (38.8)	80 (42.1)	$\chi2(1)=0.41$	0.524
≥ 41 years	98 (61.3)	110 (57.9)		
Tumor location				
Ankle and foot	7 (4.4)	8 (4.2)	$\chi2(11)=14.53$	0.205
Arm	9 (5.6)	4 (2.1)		
Back	37 (23.1)	62 (32.6)		
Chest Wall	5 (3.1)	10 (5.3)		
Elbow and forearm	10 (6.2)	15 (7.9)		
Hand	34 (21.2)	22 (11.6)		
Knee	6 (3.8)	7 (3.7)		
Leg	6 (3.8)	6 (3.2)		
Pelvis	6 (3.8)	5 (2.6)		
Shoulder	6 (3.8)	17 (8.9)		
Spine	2 (1.2)	3 (1.6)		
Thigh	19 (11.9)	31 (16.3)		
Tumor origin				
Fat Producing	93 (58.1)	139 (73.2)	$\chi2(9)=21.31$	0.011
Fibrous Producing	11 (6.9)	3 (1.6)		
Glomus body	6 (3.8)	6 (3.2)		
Muscle Origin	4 (2.5)	4 (2.1)		
Neural crest	1 (0.6)	0		
Primitive mesenchymal cells	0	1 (0.5)		
Small Round Blue Cell	1 (0.6)	6 (3.2)		
Synovial origin	34 (21.2)	22 (11.6)		
Tumor like origins	6 (3.8)	4 (2.1)		
Unknown Origin	4 (2.5)	5 (2.6)		
Histopathological returned tissue finding				
Lipoma	93 (58.1)	136 (71.6)	$\chi2(12) =21.31$	0.033
Gaint cell tumor of the tendon sheath	34 (21.2)	22 (11.6)		
Glomus tumor	6 (3.8)	6 (3.2)		
Tumor Like	6 (3.8)	4 (2.1)		
Desmoid tumor	8 (5)	2 (1.1)		
Liposarcoma	4 (2.5)	5 (2.6)		
Synovial sarcoma	3 (1.9)	5 (2.6)		
Leiomyosarcoma	3 (1.9)	3 (1.6)		
Lymphoma	1 (0.6)	3 (1.6)		
Plasmacytoma	0	3 (1.6)		
Clear cell sarcoma	1 (0.6)	0		
Myxoma	0	1 (0.5)		
Pleomorphic sarcoma	1 (0.6)	0		

The table-6 displays the resulted findings from analyzing the association between patients' age groups with their measured soft tissue tumor characteristics. The findings showed that there was no statistically significant association between soft tissue tumor-bodily locations with the patients' ages. However, tumor origins differed significantly between patients aged above and below forty years, p=0.004. Patients older than forty were more likely to develop fat producing and muscle originating tumors but less likely for synovial originating tumors compared to younger patients.

Table 6: Bivariate analysis of the patients' age groups for statistically significant differences in soft tissue tumors findings.

	Patients Age		Test statistic	p-value
	≤ 40 years	≥ 41 years		
Tumor location				
Ankle and foot	10 (7)	5 (2.4)	$\chi2(11)=14.53$	0.205
Arm	1 (0.7)	12 (5.8)		
Back	38 (26.8)	61 (29.3)		
Chest Wall	6 (4.2)	9 (4.3)		
Elbow and forearm	14 (9.9)	11 (5.3)		
Hand	28 (19.7)	28 (13.8)		
Knee	7 (4.9)	6 (2.9)		
Leg	3 (2.1)	9 (4.3)		
Pelvis	3 (2.1)	8 (3.8)		
Shoulder	14 (9.9)	22 (10.6)		
Spine	1 (0.7)	4 (1.9)		
Thigh	17 (12)	33 (15.9)		
Tumor origins				
Fat Producing	85 (59.9)	147 (70.7)	$\chi2(9)=24.04$	0.004
Fibrous Producing	9 (6.3)	5 (2.4)		
Glomus body	6 (4.2)	6 (2.9)		
Muscle Origin	0	8 (3.8)		
Neural crest	1 (0.7)	0		
Primitive mesenchymal cells	0	1 (0.5)		
Small Round Blue Cell	1 (0.7)	6 (2.9)		
Synovial origin	30 (21.1)	26 (12.5)		
Tumor like origins	6 (4.2)	4 (1.9)		
Unknown Origin	4 (2.8)	5 (2.4)		
Histopathological returned tissue finding				
Lipoma	88 (62)	141 (67.8)	$\chi2(12) =24.11$	0.014
Gaint cell tumor of the tendon sheath	30 (21.1)	26 (12.5)		
Glomus tumor	6 (4.2)	6 (2.9)		
Tumor Like	6 (4.2)	4 (1.9)		
Desmoid tumor	5 (3.5)	5 (2.4)		
Liposarcoma	1 (0.7)	8 (3.8)		
Synovial sarcoma	4 (2.8)	4 (1.9)		
Leiomyosarcoma	0	6 (2.9)		
Lymphoma	0	4 (1.9)		
Plasmacytoma	0	1 (0.5)		
Clear cell sarcoma	1 (0.7)	0		
Myxoma	0	1 (0.5)		
Pleomorphic sarcoma	0	1 (0.5)		

Secondary to lack of comparative data in Jordan, we compared our results with the regional resources. A study was conducted by Öztürk R et al in a tertiary clinic from different regions of Turkey between January 2002 and July 2013, they evaluated retrospectively 3133 patients who presented with presumed bone and soft tissue tumors. Soft tissue tumors were founded in 32% of the histopathologic examination of the presumed musculoskeletal tumors. According to Öztürk's study, the most common benign soft tissue tumors were lipoma (22%), giant cell tumors (16%) and ganglion cyst (16%), while the most common malignant soft tissue tumors were Liposarcoma (16%) followed by synovial sarcoma (16%) and malignant mesenchymal tumors (13%); respectively.[8]

Similarly, Neyisci C et al reviewed 552 patients who were surgically treated for musculoskeletal tumors in a tertiary military hospital in Turkey between 2009 and 2014. They found that the most common primary benign soft tissue tumors were lipoma, ganglion, and giant cell tumor of the tendon sheath, while the most common malignant soft tissue tumors were liposarcoma and synovial sarcoma, respectively.[9]

A comparative finding was identified by Solooki S et al who reviewed 426 pathologic reports from 1997 to 2008 in Shiraz University Orthopedic Hospitals which are the main referral centers for musculoskeletal tumors in the south of Iran.[10] Accordingly, the findings in our study were comparable to the regional resources.

CONCLUSION

Fat origin tumors are the most common musculoskeletal soft tissue neoplasm. Lipoma was the most common benign tumor (65.4 %) diagnosed in our 350 - patient sample, followed by giant cell tumors of tendon sheath (16%) and glomus tumor (3.4%) respectively. Regarding soft tissue sarcoma, Liposarcoma was the most common (2.6%), followed by synovial sarcoma (2.3%) and Leiomyosarcoma (1.7%).

The back was the most common tumor's location (28.3%), while hand, thigh and shoulder had the following frequency: 16 %, 14.3 % and 10.3 % respectively. Leg, pelvis, spine and thigh origin of soft tissue tumors in addition to the tumors arising from muscles; small round cells and those of unknown origin were founded to be significantly more predicted for malignancy. Age older than forty years were significantly more predicted for malignant soft-tissue tumors as well.

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