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RESEARCH ARTICLE

Evaluation of Prognostic Factors for Local Recurrence of Extremity Soft Tissue Sarcoma: Observational Study in a Tertiary Care Hospital

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Abstract

Background: Soft tissue sarcoma (STS) is a rare (1%) and heterogenous group of mesenchymal malignancies. In most of the cases (60%), it affects the extremities. Surgery is established as the mainstay of treatment, which is often complicated by local recurrence in 10-20% of the patients. This number is relatively high in a densely populated country like ours. To address this issue, extensive knowledge about the prognostic factors for local recurrence is necessary, which is unfortunately scarce for our population due to the need for more data in the literature. So, we aim to evaluate the impact of prognostic factors on local recurrence for better management and improved local recurrence-free survival of our patients.

Aim of the study: To evaluate the prognostic factors associated with local recurrence of extremity soft tissue sarcoma presenting at NICR&H.

Methods: It was a cross-sectional study conducted among 70 patients presented with local recurrence of extremity soft tissue sarcoma at the Department of Surgical Oncology in NICR&H from January 2021 to December 2021. Multiple clinicopathological and treatment-related prognostic factors were analyzed along with margin status and local recurrence using univariate and multivariate analysis.

Result: Among the 70 patients, the majority (71.4%) were below 50 years having a recurrence at the lower limb (67.15%). Pre-operative tissue diagnosis was done in only 18 (26%) patients. Forty-five of our patients (64%) underwent unplanned excision, with a significant relation (p=.03) with local recurrence. The mean time to recurrence was 13.54±6.93 months. Multiple recurrences were present in 21 (30%) patients. Fibrosarcoma (18.57%) was the most common histopathology, followed by UPS (17.14%) and Synovial Sarcoma (14.29%). Adjuvant Chemotherapy (p=.004) and Radiotherapy (p=0.017) were significantly related to local recurrence.

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In association with margin status, tumour size, type of surgery, and pre-operative tissue diagnosis were statistically significant prognostic factors. Multivariate Cox regression analysis showed Marginal status, adjunct Chemotherapy, and Radiotherapy as the statistically significant prognostic factors. Moreover, survival analysis showed that those with a non-involved margin have better local recurrence-free survival.

Conclusion: The study result suggests that not all the prognostic factors for local recurrence of extremity STS are significant for our population. Tumour size, adjuvant Chemotherapy, adjuvant Radiotherapy, pre-operative tissue diagnosis, type of surgery and margin status are the most significant prognostic factors. Addressing these factors in our patients will undoubtedly improve the current scenario with local recurrence. Further large-scale study and long-term follow-up will be required to validate these findings.

Keywords: Evaluation, Prognostic Factors, Local Recurrence, SoftTissue Sarcoma, Observational Study, and Tertiary Care.

1. Introduction

Soft-tissue sarcomas (STS) form a large and heterogeneous group of mesenchymal extra-skeletal malignancies that account for <1% of all malignant tumours in the general population with an annual age-adjusted incidence of 2 per 100,000 (1% of adult solid neoplasms and 7% of pediatric solid neoplasms) [1]. STS can develop virtually anywhere in the body; however, most tumours originate in an extremity (59%), the trunk (19%), the retroperitoneum (15%), or the head and neck (9%) [2].

Rhabdomyosarcoma is the most common STS in children, whereas undifferentiated pleomorphic sarcoma is the most common in adults [3]. Despite the variety of histologic subtypes of around 50 types [4], soft tissue sarcomas are grouped at the clinical level because of parameters such as location, growth pattern and likelihood of recurrence, patient age, metastases, therapy, and prognosis [5].

Patients with STS are at significant risk of local recurrence and lung metastasis. Locally recurrent disease is defined as a tumour at a site previously treated for an extremity STS more than 3 months after initial local therapy [6]. Local recurrence rates are reportedly 80-90% when simple resection is performed with inadequate or positive margins [7].

Before the advent of combined modality treatment, local recurrence rates as high as 40- 60% were reported [6]. However, with sophisticated imaging modalities, adjuvant radiotherapy, and appropriate limb salvage techniques, postoperative local recurrence rates of soft tissue sarcomas have improved from 7- 15% [8]. Surgical margin, size, grade, tumour histology, location, and the presence or absence of adjuvant therapy are known risk factors for local recurrence [9,10]. It is also reported that surgical margin and tumour location are risk factors for local recurrence in patients with soft tissue sarcomas. Moreover, patients with local recurrences are reportedly predisposed to future recurrences [11], which are difficult to treat and have higher amputation rates during surgical resection than those with primary tumours [12].

When these lesions are diagnosed and biopsied in an institution other than a referral centre, errors (such as incomplete or inadequate excision) may occur because of unfamiliarity with this disease, and alterations in the treatment plan are often required. The rate of such unplanned excision being referred to specialist centres can be up to 52% [13].

Initial inadequate surgical treatment results in more extensive surgery involving free-tissue transfers and sometimes amputation at the time of definitive care. The major therapeutic goals are long-term survival, avoidance of local recurrence, maximizing function and minimizing morbidity. Landmark trials conducted in the 1970s and 1980s at the National Cancer Institute showed equivalent survival outcomes between limb amputation and limb-sparing surgery combined with radiotherapy (RT) [14].

Amputation was common in the past, whereas current clinical practice entails limb-sparing resections in the majority of patients without compromising survival[15].

Adjuvant radiotherapy and chemotherapy (for metastatic disease) may also have a role in the treatment of selected patients [16]. Due to their heterogeneous nature and rarity, most clinicians and pathologists have limited experience in the diagnosis and complex multimodality treatment of these lesions in developing countries [17]. However, despite apparently complete

resections, one-third of patients with extremity STS suffer recurrence, typically within two years [18]. Several risk factors associated with recurrence have repeatedly been reported in the literature, including histologic subtype, tumour location, size, depth, grade, and surgical margin [19]. Treatment of STS should be centralized in tertiary centres with devoted multidisciplinary teams comprising oncologists, orthopaedic surgeons, radiologists and pathologists, and patients should be referred prior to any biopsy or excision.

Sarcomas generally have a poor prognosis, with a five-year overall survival rate hovering around 36%-58% [20]. Overall survival is impacted by various prognostic factors that include histologic subtype, grade, and completeness of tumour resection. Since surgical resection is the mainstay of management, different patterns of resection, including the employment of complex compartmental resection, are often required and are associated with varying complication rates and postoperative outcomes.

Due to the paucity of data elucidating the outcomes of extremity soft tissue sarcoma (eSTS) in developing nations such as Bangladesh, there is an unmet need to analyze these parameters as they pertain to the recurrence of eSTS. The aim of the present study, therefore, is to delineate these demographics and surgical and tumour-related parameters that contribute to local recurrence so that we can specifically address those factors significant for our population.

2. Methodology and Materials

The cross-sectional observational study was undertaken on the patients diagnosed with recurrent extremity soft tissue sarcoma presenting at the OPD or indoor unit of the Department of Surgical, Medical or Radiation Oncology, NICR&H, Dhaka from the period of January 2021 to December 2021 with approval by the Institutional Ethical Review Committee (ERC).

All the patients who presented with recurrence of extremity soft tissue sarcoma were taken into consideration for further scrutiny.

Previous valid documents like preoperative diagnosis or imaging, operative notes, post-operative histopathology reports and imaging documents were reviewed, then the patients were clinically examined and assessed for distant metastasis, and lastly, they were selected for the study according to eligibility criteria. Among the 117 patients, a total of 70 patients were finalized to participate in the study depending on inclusion and exclusion criteria.

- Inclusion Criteria:
- Any patient diagnosed with recurrent soft tissue
- sarcoma of the extremities after 6 months of initial local therapy.
- It was diagnosed as a case of recurrent extremity sarcoma by a multidisciplinary tumour board at NICR&H.
- Exclusion Criteria:
- Patients with non-sarcoma pathology, as well as patients with solitary fibrous tumours or with uncertain malignancy in the extremity.
- Patients with distant metastasis.
- Patients need valid documents or records.
- Patients and or attendants are unwilling to give consent.

All patients were informed vividly regarding the study procedure, and informed written consent was obtained. The patient's demographic characteristics, preoperative investigation findings, and operative and histopathological details were recorded in the data collection sheet.

The demographic data variables for analysis include age, gender, occupation and area. Age was grouped as above and below 50 years for analysis [21]. After taking history, conducting clinical examinations, and conducting relevant investigations, tumour staging at presentation was recorded in the data collection form.

Their previous valid clinical notes, imaging data and histopathological reports after excision were analyzed for tumour characteristics associated with recurrence, e.g., tumour size (T), nodal status (N), histological Type, grading (G) according to the FLNCC and margin status. Then,

Staging was done accordingly. Tumor size was grouped as >10cm or < 10 cm for analysis. Grading was grouped as Low grade (G1) or High grade (G2 and G3) according to the AJCC staging system [20].

Margin was grouped as involved or not involved. Previous operative notes were evaluated for variables associated with surgery, e.g., Type of surgery, and comments on Type of resection (R) were recorded.

Time to recurrence at the presentation from the last definitive treatment was recorded from hospital documents, and a history of multiple recurrences was

noted in the datasheet. Then, patients were grouped depending on whether they received adjuvant chemotherapy, radiotherapy, or both. All the recorded data were then preserved for processing.

3. Data Processing and Analysis

Data was collected, compiled, and edited before being input into a customized app via Google Forms and App Sheets. The information was then transferred to Excel and converted into an SPSS file for analysis using SPSS version 25.

Results were presented in tables and graphs with clear descriptions. Continuous data was expressed as mean±SD and categorical data as frequency and percentage. Statistical tests such as chi-square and independent paired t-tests were employed for comparisons.

Significance was determined at $p<.05$ with a 95% confidence interval. Event survival (recurrence) was depicted using a Kaplan-Meir curve, and Cox regression analysis was conducted for multivariate analysis of significant factors.

4. Result

A total of 70 patients with recurrent sarcoma of the extremities were enrolled on the study. The results are shown in the following tables and figures. Out of 70 patients, 50(71.4%) were above 50 years, 40(52.1%) were males, and 30(47.9%) were females, with a male-female ratio of 1.33:1. And among the males, 17(42.5%) were Farmers in Occupation. Around half of the patients were taking tobacco (52.86%), and most of them (58.57%) lived in rural areas (Table 1).

According to Clinical presentation, 47(67.15%) patients presented with lower limb recurrence, and among them, the thigh is the highest (43%) according to location. Most of the patients presented with a lump (78%), pain (38.57%) and weakness (4.2%) (Table 2). Moreover, among them, 50% (n=9) of patients underwent FNAC as their tissue diagnostic investigation (Figure 1). Almost 70% of the patients did not undergo any IHC during management, and only 1(1%) patient underwent preoperative IHC, and the rest, 20(29%) of the patients, had post-operative IHC examination (Figure 2). As for surgical procedures, only 18(26%) patients underwent wide excision, and the rest were either Unplanned (34%) or Simple Excision (40%).

We consider wide local excision and simple excision with preoperative tissue diagnosis as planned surgery; the rest are considered Unplanned Surgery (Figure3). According to type of surgery and its association with time to recurrence, there is a significant (p=.038) difference between planned and unplanned d surgery in locally recurrent soft tissue sarcoma patients (Table3).

Only 30% of patients had multiple recurrences previously (Figure 4). Adjuvant Chemotherapy (CT) and Radiotherapy (RT) were received by 26(37%) and 4(5.7%) patients, respectively. The majority of the patients had not received adjuvant CT and RT, and it had a statistically significant impact on local recurrence (Table 4).

According to Histopathology, Fibrosarcoma, undifferentiated pleomorphic sarcoma, and synovial sarcoma were the most common histology, comprising about 18%, 17% and 14% of the total samples (Table5).

From Cox multivariant regression survival analysis with time to recurrence, we can see that adjuvant CT, RT and Margin status are the statistically significant factors associated with Local Recurrence (Table 8).

Kaplan Meier curve of time to an event (Local Recurrence) was used to show the local recurrence-free survival depending on margin status, and it is seen that those with a non-involved margin have better recurrence-free survival (p=005) in comparison to those with involved margin (Figure 5).

Table 1. *Distribution of patients according to demographic characteristics (N=70).*

Variable	Frequency (n)	Percentage (%)	P value
Age			
<50	50	71.4	0.94
>50	20	28.6	
Gender			
Male	40	52.1	0.85
Female	30	47.9	

Occupation			
Housewife	23	32.9	-
Farmer	17	24.3	
Student	11	15.7	
Service Holder	9	12.9	
Businessman	9	12.9	
Teacher	1	1.4	
Tobacco Taking			
Yes	37	52.86	0.63
No	33	47.14	
Area			
Urban	29	41.43	0.65
Rural	41	58.57	

Table 2. *Distribution of patients according to disease presentation (N=70).*

Variable	Frequency (n)	Percentage (%)
Side		
Right	44	62.86
Left	26	37.14
Limb		
Upper	23	32.85
Lower	47	67.15
Site		
Thigh	30	45.86
Shoulder	13	18.57
Leg	11	15.71
Gluteal	6	8.57
Forearm	5	7.14
Arm	5	7.14
Presentation		
Lump	55	78.57
Pain	27	38.57
Weight loss	1	1.4
Weakness	3	4.2

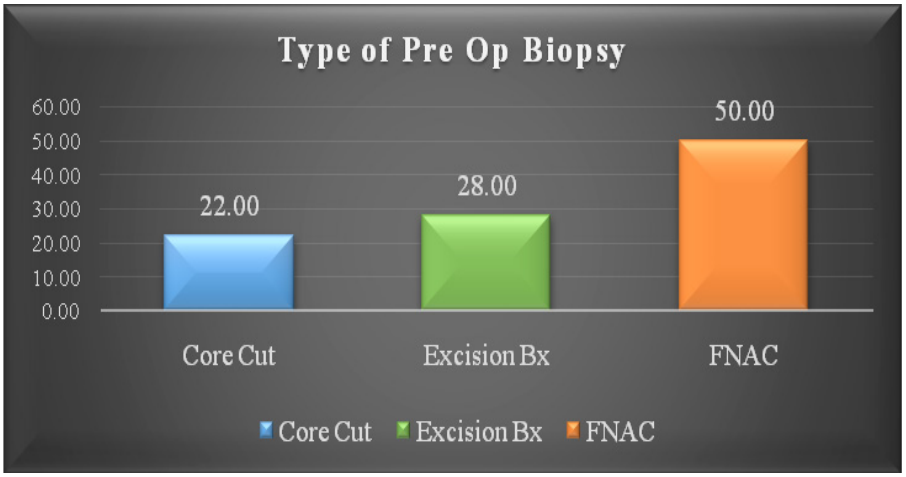

Figure 1. *Distribution of patients according to biopsy method (N=18).*

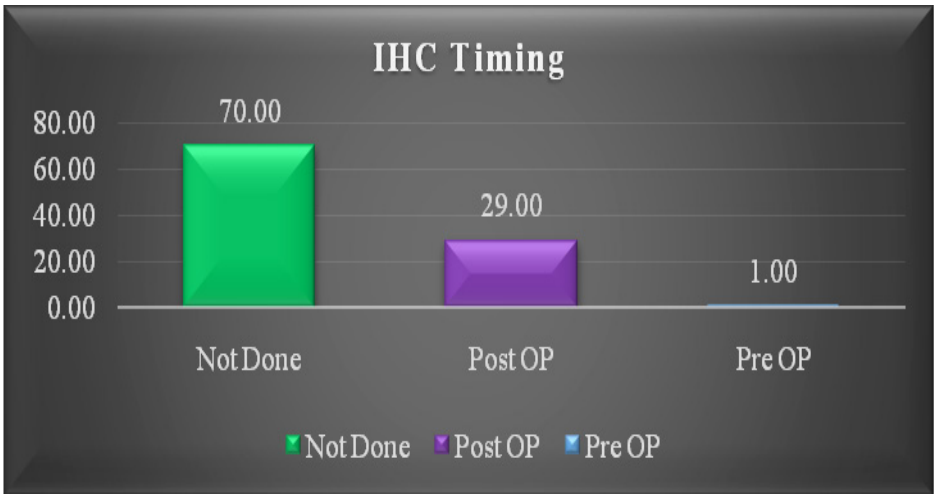

Figure 2. *Distribution of Patients According to timing of IHC (N=70).*

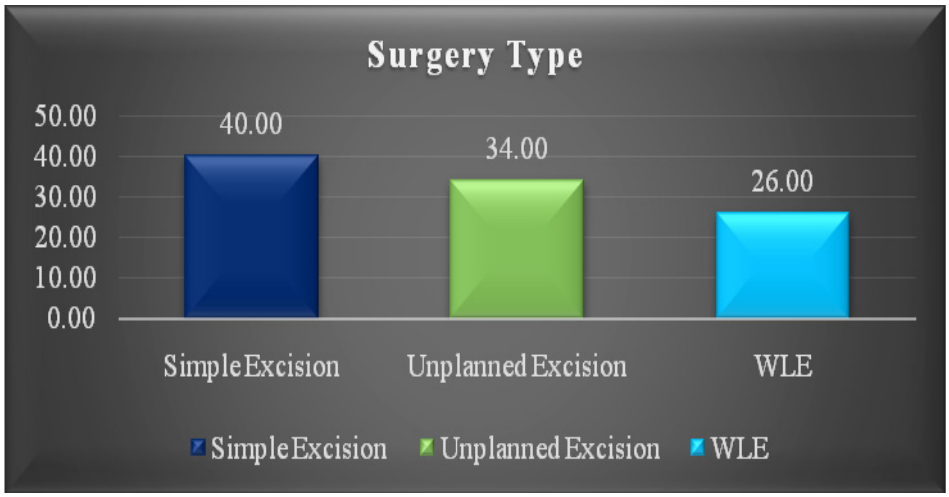

Figure 3. *Distribution of patients according to surgical procedure (N=70).*

Table 3. *Distribution of patients according to type of Surgery (N=70).*

Variable	Frequency (n)	Percentage (%)	Recurrence Time (Mean ±SD)	P value
Type of Surgery				
Planned	25	36	15.84±8.2	0.038
Unplanned	45	64	12.27±5.8	

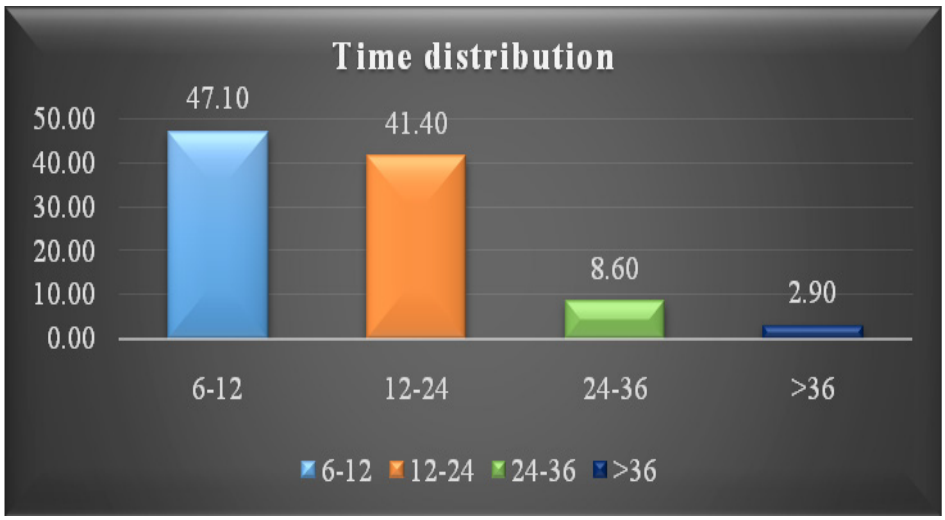

Figure 4. *Distribution of patients according to time of recurrence (N=70).*

Table 4. *Distribution of patients according to adjuvant therapy (N=70).*

Variable	Frequency (n)	Percentage (%)	P value
Chemotherapy			
Yes	26	37	0.004
No	44	63	
Radiotherapy			
Yes	4	5.7	0.017
No	66	94.3	
CT+RT			
Yes	3	4.3	0.007
No	67	95.7	

Table 5. *Distribution of patients according to Histopathology (N=70).*

Variable	Frequency (n)	Percentage (%)
Histopathology		
Fibrosarcoma	13	18.57
UPS	12	17.14
Synovial sarcoma	10	14.29
Liposarcoma	9	12.86
Spindle Cell Sarcoma	8	11.43
MPNST	6	8.57
Rhabdomyosarcoma	4	5.71
Epithelioid Sarcoma	3	4.29
Ewing's sarcoma	2	2.86
Leiomyosarcoma	2	2.86
DFSP	1	1.43

Table 6. *Distribution according to histopathological characteristics (N=70).*

Variable	Frequency (n)	Percentage (%)	P value
Size			
<10	51	72.9	0.022
>10	19	27.1	
T Stage			
T1	9	12.86	0.022
T2	42	60	
T3	17	24.29	
T4	2	2.86	
N Stage			
N0	70	100	
N1	0	0	
Grade			
GX	16	22.9	0.6
Low Grade	16	22.9	
High Grade	38	54.3	
Staging			
Stage I	32	45.7	0.288
Stage II	5	7.1	
Stage III	33	47.1	

Margin			
Involved	47	67.14	0.008
Not Involved	23	32.86	

Table 7. *Association of factors with margin status (N=70).*

Variables	Margin Status				Total		P value
	Involved (N=47)		Not involved (N=23)				
	n	%	n	%	n	%	
Age Group							
<55	40	57.1	17	24.3	57	81.4	0.258
>55	7	10	6	8.6	13	18.6	
Limb							
Upper	16	22.9	7	10	23	32.9	0.763
Lower	31	44.3	16	22.9	47	67.1	
Tobacco Taker							
Yes	26	37.1	11	15.7	37	52.9	0.555
No	21	30	12	17.1	33	47.1	
Pre-OP Tissue Dx							
Yes	8	11.4	10	14.3	18	25.7	0.017
No	39	55.7	13	18.6	52	74.3	
Surgery Type							
Planned	12	17.1	13	18.6	25	35.7	0.011
Unplanned	35	50	10	14.3	45	64.3	
Tumour Size							
<10	38	54.3	13	18.6	51	72.9	0.032
>10	9	12.9	10	14.3	19	27.1	

Table 8. *Multivariate Cox Analysis for LRFS.*

Factors	LRFS	P value
	Hazard Ratio (95% CI)	
Age	0.992(.974-1.011)	0.409
Anatomical Site	0.896(.512-1.567)	0.7
Pre op tissue Dx	0.385(.123-1.210)	0.102
Type of Surgery	1.981(.660-5.948)	0.223
Previous Recurrence	0.771 (.432-1.377)	0.38
Adjuvant CT	2.782(1.523-5.082)	0.001
RT	3.420(1.056-11.077)	0.04
Tumour Size	0.966(.531-1.759)	0.91
Margin Status	0.27(.133-.547)	0

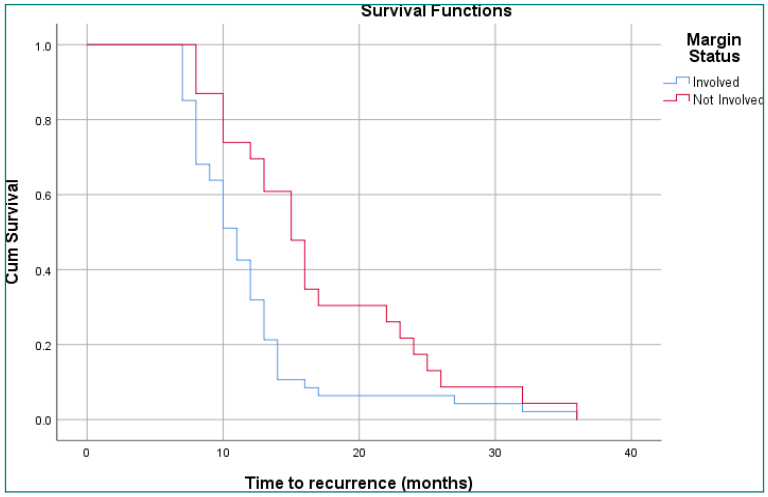

Figure 5. *Kaplan Meier Curve for Local recurrence free Survival analysis (N=70).*

5. Discussion

The purpose of this observational study is to evaluate the prognostic factors associated with local recurrence of STS, to find out their statistical significance in the context of our population and to compare them with the literature data from other populations. STSs are a rare and heterogeneous group of malignant tumours arising from the mesenchymal tissue.

As per cancer statistics in the United States, the incidence of STSs is approximately 1%, whereas incidence data on STSs in Bangladesh are unknown as studies are limited and there is no updated registry with patient follow-up [3]. STS incidence increases with age, with the reported median age in Western literature falling in the sixth decade [22]. In our study, the median age is 40 years, which is comparable to that of other studies from different parts of India, which is 45 years.

The median age in the Indian subcontinent is a decade earlier than that in the developed countries. This early occurrence may be due to differing age spectrums of the population in developed countries and Bangladesh, as a significant proportion of the Bangladeshi population is young. A slight male preponderance with a male-to-female ratio of 1.3:1, similar to other studies, is reported, which is 1.4:1 [23].

Occupational factors such as job type, industry, and exposure to chemicals such as herbicides and chlorophenols have been suggested as risk factors for sarcomas [24]. The AGRICAN cohort is a prospective study of 181,842 individuals enrolled in 2005-2007, where the risk of sarcomas was increased in several farming activities due to benzene derivatives [25]. STS can occur throughout the body; however, the majority (60%) occur in the extremities [26]. With reason unexplained, the lower limb is a more preferred site of occurrence, with an incidence of almost 72%. Probably, the large bulk of soft tissue in the thigh and leg compartments is the reason [27]. In our study, the lower limb consists of almost 68% of all recurrence, which is similar to the previous studies. In this study, nearly 65% of the patients underwent an unplanned excision.

This finding is higher than other studies, which range from 14.7% to 53% [28]. It is also higher than the findings from a study in the Indian context by Tiwari et al which is 41% [21]. Our finding is also statistically significant (p=.038), which implies that it is responsible for the higher rate of recurrence in our population. The average time to recurrence after initial surgical management is 22 months (range, 2-75 months), according to the literature [29].

However, in our study, it is 13.54±6.93 months, which is shorter than average. Incomplete treatment and lack of initial proper management may explain our shorter recurrence-free interval. Adjuvant Chemotherapy (CT) and Radiotherapy (RT) were received by 26(37%) and 4(5.7%) patients, respectively. The majority of the patients had not received adjuvant CT and RT, and it had a statistically significant impact on local recurrence.

This finding is consistent with other relevant studies by various authors [30,31]. Radiotherapy or chemotherapy in a perioperative setting improves outcomes in tumours of size ≥5cm, deep-seated, or high grade [32]. Preoperative therapy is associated with increased ease of resection, decreased local recurrence, reduced late toxicity, and a trend toward improved survival outcomes [33]. Most studies [34], like ours, found that radiotherapy reduces the LR rate; however, the characteristics of tumours for which radiotherapy is beneficial vary. Kaytan et al. reported

an effect only in high-grade tumours, while Jebsen et al. reported effects in low-grade tumours also [35,36]. In our study, Fibrosarcoma, undifferentiated pleomorphic sarcoma and synovial sarcoma were the most common histology, comprising about 18%, 17% and 14% of the total samples.

However, our result is different from that of the Indian counterpart, which may be due to the lack of IHC diagnosis. With standardization of diagnostic criteria and extended immunohistochemistry, some of the undifferentiated pleomorphic sarcomas and all of the spindle cell sarcomas can be reclassified into specific subtypes. We did not find any significant difference in the oncological outcome among the more common histopathological varieties. The prognostic impact for local recurrence is still controversial, with some larger studies reporting an impact, while others report no impact [37,38,39].

Most studies analyze tumour size as a categorical variable, often with different cutoff values, which might explain the difference in impact on local recurrence. This is supported by Zagars et al., who report that there is a significant impact on Local recurrence when 5 cm is used as a cutoff value but not when 10 cm is used [40]. However, interestingly, the cutoff value in our population is 10 cm instead of 5 cm, which is consistent with a similar study by Tiwari et al. from India [21].

More than half of our patients (60%) had tumours of 5 to 10 cm (T2), reflecting a delay in referral and healthcare-seeking behaviour of our patients as compared to the Western population [1]. It was interesting to note that in our study, a cutoff of 10 cm tumour size showed a significant difference in oncological outcome, which is local recurrence (p=.022). While that of 5 cm did not do so. All this leads us to believe that tumour size subgrouping beyond 5 cm is important to define high-risk groups and support our results seen with tumour sizes more than 10 cm.

The histological grade is, along with tumour size and surgical margin, the most well-established prognostic factor. The overall purpose of grading systems is, based on the histological parameters, to evaluate the degree of malignancy and thus identify patients at greater risk of local recurrence. Even though different factors and different cutoff values are used in the different grading systems, all systems have proven to correlate with the risk of local recurrence in patients [41]. In our study, we could not find a significant relationship between low and high grades of sarcoma and recurrence. This may be due to the fact that a large portion of our samples (23%) had GX grading, which, if properly identified, could have an impact on statistical significance.

Patients with involved surgical margins are statistically significant for local recurrence (p=.001) in our study. Moreover, those with a non-involved margin have a better local recurrence-free survival (p= .005). This was consistent with the study of Liu et al. and Stefanovski et al., which said that the surgical margin can be a predictive factor for recurrence [19,42]. If the distance of the surgical margin free from the tumour is greater, the recurrence rate will be lower. This might happen because patients with high stage have a higher risk of their surgery not obtaining the tumour-free edge of the incision. Positive surgical margins are a strong prognostic factor of LR in patients with STS in extremities.

The minimum margin distance required to reduce the risk of LR of high-grade STS is still debatable [43]. Liu et al. had previously identified a 10 mm margin to be an oncologically safe margin [19]. A recommendation from NCCN stated that adjuvant radiotherapy was given to patients with soft tissue sarcomas with resection of less than 1 cm from the tumour since the minimum margin spacing needed to reduce the risk of LR of high-grade soft-tissue sarcoma remains undefined [4].

Limitations of the study:This study has several limitations. Firstly, this study has a relatively small sample size. Secondly, this is a cross-sectional observational study with a minimum follow-up of one year. We are aware that the recurrence would occur in the first 2-5 years. Unfortunately, a large number of patients fail to comply with the follow-up program.

For instance, some preferred to discontinue the treatment and prefer alternative non-medical treatment. Thirdly, it is a single-centre study, which might be subjected to bias. To improve the outcome of the study, a multi-centre study with a prospective design and a larger sample size should be conducted. Lastly, due to the pandemic, many patients could not come for follow-up or timely treatment, which might have affected the results.

6. Conclusion

This study investigates local recurrence in extremity soft tissue sarcomas (STS) and identifies unique prognostic factors in the population. Notably, individuals under 50 years old are more affected, with no significant link to tobacco use. Recurrence often occurs in the lower limb, especially the thigh,

and is associated with unplanned excisions and lack of pre-operative tissue diagnosis. Adjuvant therapy, including radiotherapy and chemotherapy, plays a crucial role in preventing recurrence, but awareness is lacking. Tumor size correlates with margin involvement, impacting recurrence. The population exhibits a shorter time to recurrence, emphasizing the need for rigorous follow-up and education on timely adjuvant therapies. The study recommends a large-scale case-control study to address critical prognostic factors.

7. References

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