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The efficacy of re-excision after unplanned excision for synovial sarcoma

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ABSTRACT

Background: This investigation studied the clinical features and outcomes of synovial sarcoma (SS) patients from a single institution.

Methods: A retrospective clinicopathologic study was conducted on 129 postoperative SS patients during 2003–2018. Kaplan-Meier curves and Cox proportional hazards regression (Cox) models were performed to determine the parameters associated with recurrence-free survival (RFS), metastasis-free survival (MFS), and cancer-specific survival (CSS) via univariate and multivariate analysis. The impact of unplanned excision (UE) and residual tumor in re-excision specimens was evaluated.

Results: The 3-year RFS, MFS and 5-year CSS were 72 %, 70 %, and 76 %, respectively. Independent factors associated with significantly inferior survival included older age, UE without re-excision, UE with residual tumors, high grade, and deep tumor for RFS, trunk-related tumor, UE without re-excision, UE with residual tumors, and deep tumor for MFS, UE with residual tumors, high grade, and deep tumor for CSS. Re-excision after UE was significantly associated with better RFS ($P < 0.001$). Residual tumors were remarkably correlated with inferior RFS ($P = 0.0012$), MFS ($P = 0.0016$), and CSS ($P = 0.048$), especially in patients at stage II (MFS: $P < 0.001$, CSS: $P = 0.0014$).

Conclusion: UE and residual tumors have a marked impact on the long-term survival of SS patients. Primary wide excision and re-excision is especially essential for patients at stage II.

1. Introduction

Synovial sarcoma (SS) is a rare tumor with a high probability of recurrence and metastasis [1]. SS is defined by a unique chromosomal translocation, t (X; 18) (p11.2; q11.2), causing the emergence of a fusion oncogene SS18-SSX1/2/4 [2]. Most sarcomas are located in the limbs' deep soft tissues, particularly in juxta-articular sites. SSs are morphologically classified as biphasic, monophasic, and poorly differentiated. The monophasic SS represents the most common histological subtype, predominantly characterized by uniform spindle cells displaying moderate cytological atypia and organized in bundles. Biphasic tumors usually display a variable amount of epithelial elements, at times forming authentic gland-like structures. Poorly differentiated tumors exhibit regions with increased cell density, and the tumor cells usually exhibit a rounded morphology [3]. In accordance with the Surveillance,

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Epidemiology, and End Results (SEER) system, the soft tissue sarcomas (STSs) yearly incidence rate is roughly 5 occurrences per 100, 000, where SS only accounts for 8–10 % of all STSs [4]. Treatment of SS is still a challenge for most surgeons due to its rarity, early diagnosis, and clinical management. Additionally, large prospective studies are absent, and the quality of research on this disease is heterogeneous.

SS is one of the most recurrent malignant STSs, characterized by a considerable metastatic potential, particularly to the lung. About 50–70 % of SS patients eventually develop metastases; of which lung metastases represent half of these metastases [5,6]. After metastasis, the 5-year survival rate is nearly 14.4 % [7]. In China, large disparities in the levels of diagnosis and treatment exist between primary and tertiary hospitals. Moreover, due to the slow-growth characteristics and their asymptomatic nature, SS are often misdiagnosed as benign tumors and incompletely resected under UE, leading to local and systemic recurrence.

Several studies have been conducted on factors for recurrence, metastasis, and cancer-specific survival of SS. Shi et al. retrospectively analyzed long-term treatment outcomes for 92 patients with SS and found that adding radiotherapy to surgery may lead to effective local control of SS patients [8]. Yaser et al. performed clinical data analysis of 51 SS patients retrospectively and discovered that negative surgical margins were the factors affecting metastasis and recurrence, while the tumor depth was the only independent variable influencing overall survival [6]. UE is the term used to describe the surgical removal of STSs without prior knowledge of its malignant characteristics. The majority of these UEs can be attributed to the combination of the rare occurrence of soft tissue sarcomas and a lack of awareness regarding them, which has long-term unpredictable impacts on patient outcomes. As one of the most common subtypes of soft tissue sarcomas, the rarity of SS might explain the high rate of UE, leading to relapse and poor prognosis. Frequently, there is an absence of suitable diagnostic and staging assessments, leading to surgical resections that overlook the recommended oncological margins for sarcomas. SS is painless, has comparatively slow growth, and more frequently occurs in the lower limbs and peri-articular tissue, which may be easily misdiagnosed as a benign tumor and undergo local resection [9]. Herein, we examined the clinical information of a large cohort of 129 patients with SS besides identified prognostic factors influencing recurrence, metastasis, and survival. In addition, we evaluated the impact of UE and residual tumors on SS patients' oncological outcomes.

2. Patients and methods

2.1. Patient population

Postoperative patients diagnosed with SS at the National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College from January 2003 to December 2018 were included. Histologic diagnosis was confirmed in accordance with the 2020 World Health Organization categorization of soft tissue and bone tumors by a group of pathologists in our hospital. Exclusion criteria were: patients without surgery; lack of pathological diagnosis; lack of TNM information or other significant information; death from causes other than cancer; combination with other malignancy.

2.2. Variables and definition

Clinical data extraction was performed by screening patients' medical records. Variables included age at diagnosis, sex, primary site (lower limb, pelvis, trunk, or upper limb), tumor size (using the largest diameter according to the surgical specimens before radiographic examination), depth (defined as deep when tumors invade the superficial fascia), histologic grade (in the basis of Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) grading system), biopsy, UE, margin status (negative, microscopic positive, or macroscopic positive, patients with amputation was defined with negative margin), lymph node involvement (suspicious lymph nodes identified during the physical examination are subjected to imaging studies to determine whether a biopsy is warranted, and finally determined by pathological examination), adjuvant radiotherapy, or chemotherapy. UE was defined as resection of the tumor performed before adequate imaging evaluation, without reaching normal tissue as margin and definitive histopathologic diagnosis. To evaluate the impact of UE and residual tumors on patients' oncological outcomes, we classified patients into four categories: (a) patients with planned wide excision, (b) patients with no re-excision after UE, (c) patients with residual tumor in the re-excision specimens after UE, (d) patients with no residual tumor in the re-excision specimens after UE. The residual tumor of "re-excision" cases was determined based on the postoperative pathology of wide excision. The margin status was determined by the postoperative pathological examination. Cases whose surgical specimens of wide resection with residual tumor were defined as microscopic positive. The origin of recurrence-free survival (RFS), metastasis-free survival (MFS), and cancer-specific survival (CSS) was the time of histological diagnosis of the obtained specimen from primary surgery or biopsy. RFS, MFS, and CSS had respective endpoints of the final follow-up or the incidence of local recurrence, distant metastasis, and disease-specific mortality, respectively. This study was censored on November 31, 2020.

2.3. Statistical analysis

The survival curves of RFS, MFS, as well as CSS were evaluated and compared utilizing the Kaplan-Meier approach and log-rank test. Multivariate analysis of RFS, MFS, and CSS was conducted with a stepwise Cox regression model. All analyses were carried out utilizing the R program (v 4.2.2). $P < 0.05$ was considered statistically significant.

3. Results

3.1. Study cohort

In total, 129 patients with SS were retrieved. Table 1 summarizes the initial features of patients. Fifty-eight (45 %) patients were males and 115 (89 %) patients were aged ≤55 years, with a median age of 36 years (range 12–64 years). In total, 91 (70 %) instances of SS were in the limbs, involving 31 patients in the upper limb and 60 patients in the lower limb. There were 24 (19 %) cases of SS in the trunk and 14 (11 %) cases in the pelvic region. It was superficial in 44 (34 %) patients and deep-seatedness in 85 (66 %) patients. The size of the tumor varied from 0.5 cm to 15 cm. Seventy-three (57 %) cases had tumors with a maximum diameter of ≤5 cm. Based on the FNCLCC grading system 84 (65 %) and 45 (35 %) cases were graded into grade 2 and 3, respectively. In addition, lymph node metastases were observed in 9 (7 %) cases. Demographics of 129 cases with SS were presented by groups of planned excision and unplanned excision (Table 2).

Table 1
Demographic and clinicopathologic characteristics of 129 cases of synovial sarcoma of the trunk and extremities.

Characteristic	Number (%)	Recurrence-free survival		Metastasis-free survival		Cancer-specific survival	
		3-year RFS (%)	P^a	3-year MFS (%)	P^a	5-year CSS (%)	P^a
Age							
≤55	115 (89 %)	74	0.049	59	0.037	80	<0.001
> 55	17 (11 %)	54		67		65	
Sex							
Male	58 (45 %)	62	0.820	67	0.950	71	0.250
Female	71 (55 %)	64		66		80	
Site							
Lower limb	60 (46 %)	84	0.039	78	0.097	81	0.140
Upper limb	31 (24 %)	60		71		78	
Trunk	24 (19 %)	66		66		69	
Pelvis	14 (11 %)	58		47		59	
Depth							
Superficial	44 (34 %)	81	0.019	86	0.006	91	0.004
Deep	85 (66 %)	67		62		46	
Size							
≤5	73 (57 %)	76	0.520	82	<0.001	88	<0.001
> 5	56 (43 %)	67		55		61	
Fusion type	110						
SSX1	78 (71 %)	64	0.3	67	0.22	72	0.46
SSX2	32 (29 %)	63		61		75	
Grade FNLCC							
Grade 2	84 (65 %)	79	0.032	84	<0.001	92	<0.001
Grade 3	45 (35 %)	57		44		46	
AJCC 8th							
II	70 (54 %)	76	0.1	84	<0.001	91	<0.001
IIIA	39 (30 %)	73		65		68	
IIIB	7 (6 %)	71		54		86	
IV	13 (10 %)	39		23		27	
Biopsy							
No	105 (81 %)	67	0.016	69	0.200	83	0.110
Yes	24 (19 %)	91		74		91	
UE							
Planned excision	25 (19 %)	92	<0.001	75	0.005	92	0.048
UE-re-excision	18 (14 %)	49		67		94	
UE-residual tumor	52 (40 %)	85		80		84	
UE + residual tumor	34 (26 %)	50		53		73	
Lymph node involved							
No	120 (93 %)	74	0.043	73	0.005	79	0.009
Yes	9 (7 %)	38		33		39	
Margin status							
Negative	76 (59 %)	85	<0.001	80	<0.001	84	<0.001
Positive	53 (41 %)	51		57		64	
Adjuvant radiotherapy							
No	56 (43 %)	69	0.950	66	0.940	67	0.330
Yes	73 (57 %)	74		73		81	
Adjuvant chemotherapy							
No	82 (64 %)	76	0.230	76	0.210	79	0.940
Yes	47 (36 %)	64		61		69	

AJCC, American Joint Committee on Cancer; CSS, cancer-specific survival; FNLCC, Federation Nationale des Centres de Lutte Contre le Cancer; MFS, metastasis-free survival (distant metastasis); RFS, recurrence-free survival; UE, unplanned excision.

[a] Log-rank test.

Table 2
Demographics of 129 cases of synovial sarcoma of the trunk and extremities by treatment patterns of planned excision and unplanned excision.

Characteristic	Number (%)		*P*
	Planned excision	Unplanned excision	
Age			1[a]
≤55	22 (88 %)	93 (87 %)	
> 55	3 (12 %)	14 (13 %)	
Sex			0.907[b]
Male	12 (48 %)	46 (44 %)	
Female	13 (52 %)	58 (56 %)	
Site			0.281[a]
Lower limb	16 (64 %)	44 (42 %)	
Upper limb	4 (4 %)	27 (26 %)	
Trunk	4 (16 %)	20 (19 %)	
Pelvis	1 (16 %)	13 (13 %)	
Depth			1[b]
Superficial	9 (36 %)	35 (34 %)	
Deep	16 (64 %)	69 (66 %)	
Size			0.062[b]
≤5	10 (40 %)	63 (61 %)	
> 5	15 (60 %)	41 (39 %)	
Fusion type	21	89	0.956[b]
SSX1	15 (71 %)	63 (71 %)	
SSX2	6 (29 %)	26 (29 %)	
Grade FNLCC			0.716[b]
Grade 2	15 (60 %)	69 (66 %)	
Grade 3	10 (40 %)	35 (34 %)	
AJCC 8th			0.274[a]
II	10 (40 %)	60 (58 %)	
IIIA	11 (44 %)	28 (27 %)	
IIIB	2 (8 %)	5 (5 %)	
IV	2 (8 %)	11 (10 %)	
Biopsy			<0.001[a]
No	2 (8 %)	103 (99 %)	
Yes	23 (92 %)	1 (1 %)	
Lymph node involved			1[a]
No	24 (96 %)	120 (92 %)	
Yes	1 (4 %)	9 (8 %)	
Margin status			0.304[b]
Negative	17 (59 %)	59 (59 %)	
Positive	8 (41 %)	45 (41 %)	
Adjuvant radiotherapy			0.771[b]
No	12 (48 %)	44 (42 %)	
Yes	13 (52 %)	60 (58 %)	
Adjuvant chemotherapy			0.117[b]
No	12 (48 %)	70 (67 %)	
Yes	13 (52 %)	34 (33 %)	

AJCC, American Joint Committee on Cancer; FNLCC, Federation Nationale des Centres de Lutte Contre le Cancer.
[a] Fisher's exact test.
[b] Chi-square test.

Although preoperative biopsy is preferred for soft tissue mass with suspicious-malignant features, the majority of patients (105/129, 81 %) did not have preoperative biopsies before primary surgery with UE performed before their presentation to our center. Skin grafts, flap transfer, vascular transplantation or free flap reconstruction were required in large surface defects after resection. Amputation was needed in 6 (5 %) cases due to significant nerve or vascular invasion. The margins status was negative in 76 (59 %) cases, and positive in 53 (41 %) cases.

Patients with large tumors, positive margin status, or local recurrences were recommended to have adjuvant radiotherapy based on postoperative pathological examination. For initially diagnosed patients with exceptionally large tumors or tumors adjacent to blood vessels and nerves., surgery is performed after achieving effective control through preoperative radiation therapy to achieve more defined margins. The external irradiation dose for conventional radiotherapy was 50 Gy/25 fractions. 73 patients (57 %) received radiation therapy, with three receiving intraoperative radiation and four receiving preoperative radiation. Three-weekly AI regimen (epirubicin + ifosfamide) was the preferred option for SS chemotherapy in our center for those patients with high risks. Chemotherapy was administered in 47 (36 %) patients, with 2 patients receiving neoadjuvant chemotherapy for local control. All the adjuvant therapy was determined by our Multi-disciplinary Team.

3.2. Survival analysis

The 3-year RFS for the entire cohort was 72 %. Forty-eight (37 %) patients developed local recurrence at a median follow-up duration of 43.9 months (range 1–174.5 months). Univariate analysis revealed that age, site, depth, grade, biopsy, UE, status, lymph node involved, and margin status had a significant relationship to 3-year RFS (Table 1). Multivariate analysis revealed that age >55 years old, UE without re-excision, UE with residual tumor, high FNCLCC grade, deep-seatedness were independent factors that were closely related to inferior RFS (Table 3).

The 3-year MFS for the whole cohort was 70 %. At the end of the follow-up, forty-nine (38 %) patients developed distant visceral metastasis at a median follow-up time of 46.2 months (range 0–110 months). Out of the 49 patients, 5 (10 %) patients exhibited lung metastases when diagnosed, 46 (94 %) patients developed lung metastases with or without metastases of the liver, brain, bone, and pleura, 1 (2 %) patient had brain metastases, and 2 (4 %) patients had liver metastases. Log-rank test results revealed that age, AJCC stage, depth, size, high FNCLCC grade, UE, lymph node metastasis, and margin status were significantly related to MFS (Table 1), and tumor in the trunk, UE without re-excision, UE with residual tumor and deep-seatedness of tumor were independently positively correlated with worse MFS (Table 3).

At the time of the endpoint, 41 (32 %) patients were deceased. The 5-year CSS for the whole cohort was 76 %, and the median survival period was 60.9 months. According to univariate analysis, age, depth, size, FNCLCC grade, AJCC stage, UE, lymph node involvement, and margin status were significantly linked to CSS (Table 1). According to multivariate analysis, UE with residual tumor, high grade, and deep-seatedness were independent factors for inferior CSS (Table 3).

Table 3
The independent prognostic factors for recurrence-free survival, metastasis-free survival and cancer-specific survival identified by multivariate analysis.

Factor	Hazard ratio (95 % CI)	*P* value
Recurrence-free survival		
Age		
≤55	Reference	
> 55	2.222 (1.047–4.716)	0.038
UE		
Planned excision	Reference	
UE-re-excision	4.588 (1.361–15.470)	0.014
UE-residual tumor	2.926 (0.908–9.423)	0.072
UE + residual tumor	3.625 (1.182–11.116)	0.024
Grade FNLCC		
Grade 2	Reference	
Grade 3	4.567 (2.179–9.572)	<0.001
Depth		
Superficial	Reference	
Deep	2.520 (1.072–5.921)	0.034
Metastasis-free survival		
Site		
Lower limb	Reference	
Upper limb	1.123 (0.518–2.431)	0.769
Trunk	2.621 (1.125–6.102)	0.025
Pelvis	1.783 (0.667–4.761)	0.249
UE		
Planned excision	Reference	
UE-re-excision	9.916 (3.068–32.051)	<0.001
UE-residual tumor	1.476 (0.457–4.766)	0.515
UE + residual tumor	5.667 (1.811–17.736)	0.003
Depth		
Superficial	Reference	
Deep	2.195 (1.054–4.574)	0.036
Cancer-specific survival		
UE		
Planned excision	Reference	
UE-re-excision	2.745 (0.987–7.633)	0.053
UE-residual tumor	1.585 (0.593–4.242)	0.359
UE + residual tumor	3.197 (1.271–8.041)	0.014
Grade FNLCC		
Grade 2	Reference	
Grade 3	3.084 (1.619–5.875)	<0.001
Depth		
Superficial	Reference	
Deep	2.293 (1.111–4.736)	0.025

CI, confidence interval; FNLCC, Federation Nationale des Centres de Lutte Contre le Cancer; UE, unplanned excision.

3.3. Impact of UE and residual tumor on clinical outcomes

104 (81 %) patients underwent initial UE. Eighteen (14 %) patients with or without adjuvant therapy underwent no extended re-excision after UE. The patients were categorized into four groups based on the combination of surgical resection patterns and residual tumors for analysis, revealing significant differences in survival outcomes among these groups (RFS: Fig. 1A, $P < 0.0001$; MFS: Fig. 1B, $P = 0.0014$; CSS: Fig. 1C, $P = 0.031$). Patients with no residual tumors after re-excision and those with planned excision have better RFS, MFS and CSS. Patients with re-excision after UE had a significantly better RFS than those without re-excision ($P < 0.001$) (Fig. 1D). Eighty-six SS patients received re-excision after UE (Table 4). The analysis revealed no statistically significant variances in terms of MFS and CSS between patient groups undergoing re-excision following unplanned excisions and those who did not (Fig. 1E, $P = 0.76$; Fig. 1F, $P = 0.783$). The long-term survival (RFS: Fig. 1G, $P = 0.0012$; MFS: Fig. 1H, $P = 0.0016$; CSS: Fig. 1I, $P = 0.048$) for UE patients with residual tumors was relatively poor.

The tumor residual rate was 40 % (34/86). The subgroup analysis was performed within patient cohorts stratified by AJCC stages II and III, as well as separately within AJCC stage II and AJCC stage III groups. The analysis indicated non-significant differences in RFS among patients diagnosed with AJCC stages II and III (Fig. 2A, $P = 0.061$), as well as within the subgroups of AJCC stage II (Fig. 2B, $P = 0.35$) and AJCC stage III (Fig. 2C, $P = 0.085$). Patients without residual tumors had relatively favorable survival than patients with residual tumors in stage II (MFS: Fig. 2E, $P < 0.001$; CSS: Fig. 2H, $P = 0.0014$), and stage II + III (RFS: Fig. 2D, $P = 0.015$). The analysis showed no statistically significant differences in MFS among patients diagnosed with AJCC stage III (Fig. 2F, $P = 0.96$). Additionally, there were no significant differences observed in CSS among patients diagnosed with AJCC stages II and III (Fig. 2G, $P = 0.19$), nor within the subgroup analysis of AJCC stage III (Fig. 2I, $P = 0.25$).

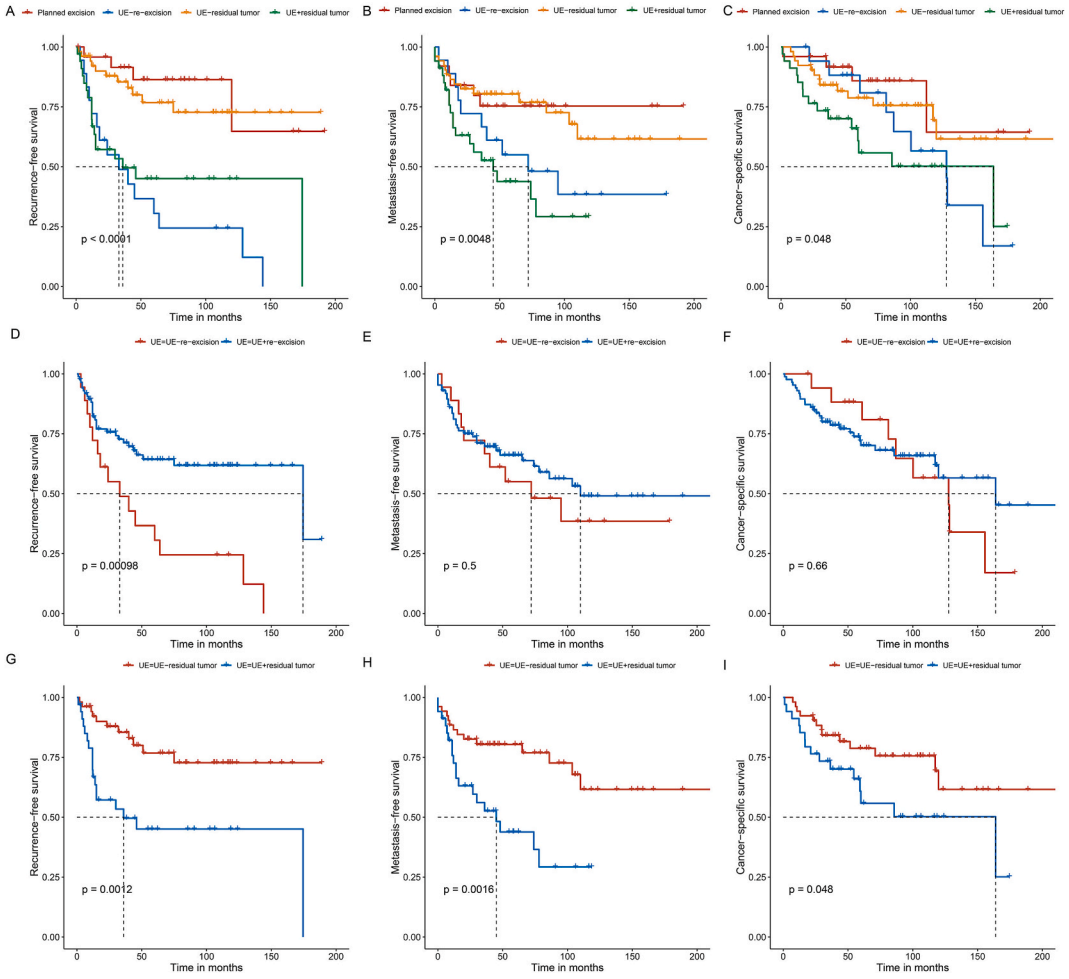

Fig. 1. (A–C) Kaplan-Meier curve for RFS, MFS and CSS based on UE for the whole cohort of 129 patients. (D–F) Kaplan-Meier curve for RFS, MFS and CSS based on re-excision for the cohort of 104 UE patients. (G–I) Kaplan-Meier curve for RFS, MFS and CSS based on residual tumor status for the cohort of 86 UE patients with re-excision. UE-re-excision, no re-excision was performed after unplanned excision; UE-residual tumor, no residual tumor was detected in the specimen of re-excision; UE + residual tumor, positive status of residual tumor in the specimen of re-excision.

Table 4
Demographics of re-excision patients with or without residual tumor (n = 86).

Characteristics	Residual tumor (−), n (%)	Residual tumor (+), n (%)	*P*
Total	52	34	
Age			1[a]
≤55	46 (88)	30 (88)	
> 55	6 (12)	4 (12)	
Sex			0.456[b]
Male	22 (42)	18 (53)	
Female	30 (58)	16 (47)	
Site			0.123[a]
Lower limb	25 (48)	11 (35)	
Upper limb	10 (19)	9 (26)	
Trunk	13 (25)	5 (15)	
Pelvis	4 (8)	7 (24)	
Depth			0.629[b]
Superficial	16 (31)	13 (38)	
Deep	36 (69)	21 (62)	
Size			0.353[b]
≤5	34 (65)	18 (53)	
> 5	18 (35)	16 (47)	
Grade FNLCC			0.157[b]
Grade 2	38 (73)	19 (56)	
Grade 3	14 (27)	15 (44)	
AJCC 8th			0.105[a]
II	32 (61)	17 (50)	
IIIA	13 (25)	8 (24)	
IIIB	3 (6)	2 (6)	
IV	4 (8)	7 (20)	
Adjuvant chemotherapy			0.286[b]
No	39 (75)	21 (62)	
Yes	13 (25)	13 (38)	
Adjuvant radiotherapy			0.512[b]
No	21 (40)	17 (50)	
Yes	31 (60)	17 (50)	

AJCC, American Joint Committee on Cancer; FNLCC, Federation Nationale des Centres de Lutte Contre le Cancer.
[a] Fisher's exact test.
[b] Chi-square test.

4. Discussion

STSs are a collection of diverse malignancies of mesenchymal origin. The pathological classification-based analysis is currently recognized as the future direction in STS research [10]. The present study retrospectively reviewed 129 patients with SS from a single institution to assess surgical therapy based on their impact on recurrence, metastasis, and survival. Moreover, we evaluated the impact of UE and residual tumors on the clinical outcomes of patients.

Several research findings have uncovered distinct risk factors linked to SS clinical outcomes. We demonstrated that the positive margin status was a significant risk factor affecting RFS and MFS and CSS, which was in agreement with the finding of Yaser et al. [6]. Previously, tumor size was widely recognized as an important factor influencing the local recurrence of STSs [11–13]. This research detected a non-significant association of large tumor size with recurrence. These results can be deceiving for two reasons. Firstly, the average tumor size of patients in our center was 5.3 cm, with a median size of 5 cm, which was easily completely resected. Secondly, patients in our center frequently received wide excision or re-excision with an adequate margin for a lower recurrence rate. In the present study, the tumor pathological grade is one of the significant independent risk factors for RFS, MFS, and CSS. The FNCLCC grading system for sarcomas is based on tumor differentiation, mitotic count, and tumor necrosis [14]. The high grade represents high aggressiveness and the metastatic potential of a tumor, predicting poor prognosis of patients.

The highest correlation for local recurrence was with the completeness of primary resection [15]. In our cohort, a majority of patients (80.6 %) underwent initial UE with inadequate surgical margins. Only 20 % of patients were initially treated with wide resection or amputation based on preoperative magnetic resonance imaging examination and pathological diagnosis by fine needle aspiration biopsy. SS is one of the most frequently misdiagnosed sarcomas based on magnetic resonance imaging, leading to UE and inadequate surgical margins [16,17]. Previous studies found that UE was not significantly related to overall survival or disease-specific survival [18–20]. Choi et al. previously reviewed 90 SS patients and demonstrated that no significant relationship between the UE group and the planned excision group was observed in RFS, MFS, and CSS [19]. However, the presence of residual tumors after local resection and its impact on survival were neglected by Choi et al. Herein, the UE and re-excision were deeply analyzed in subgroups. We found that re-excision was significantly related to a longer RFS but not MFS and CSS, which may be attributable to the radical wide re-resection in our institution. Residual tumors were present in 40 % of patients who underwent re-excision, which is lower than that reported in the previous studies [21]. In addition, UE patients with residual tumors had a remarkably inferior RFS ($P = 0.0012$), MFS

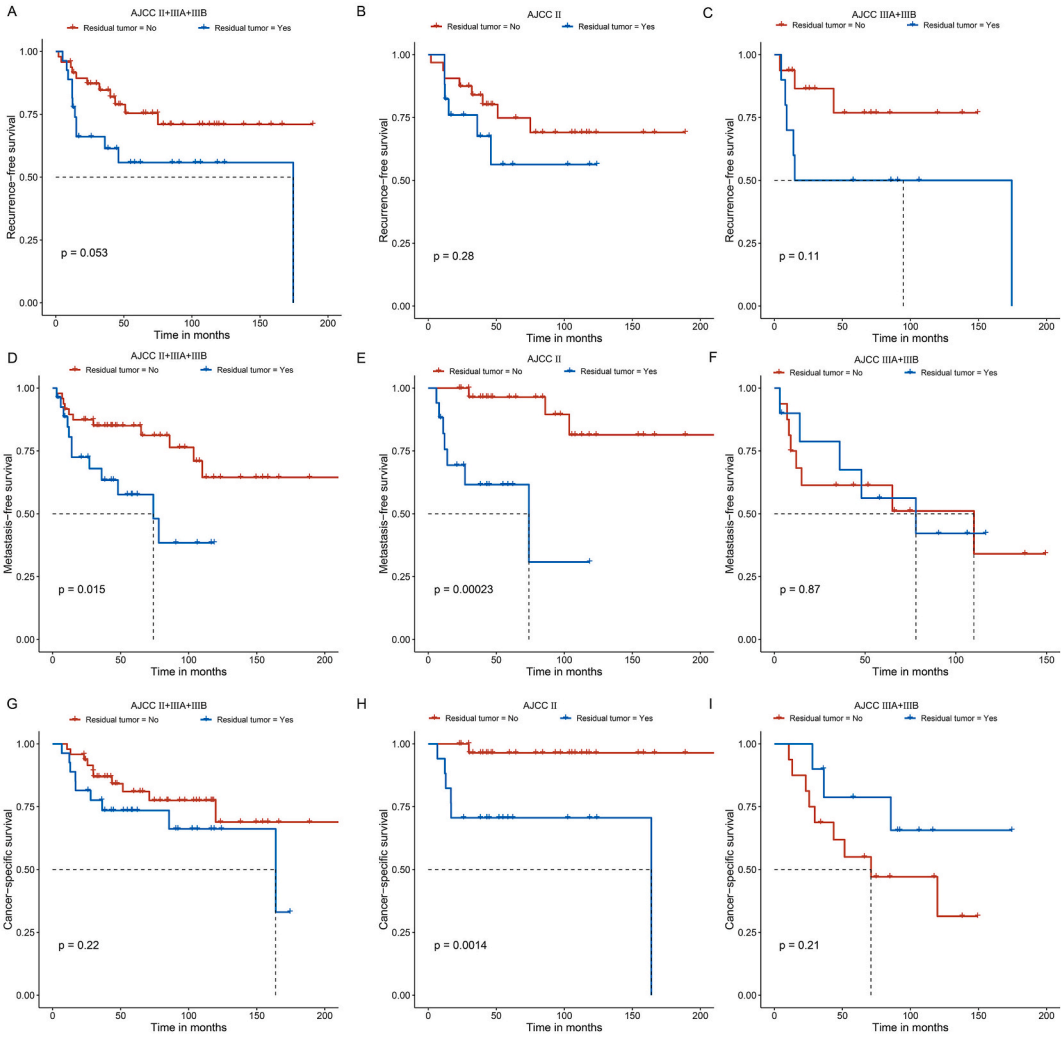

Fig. 2. (A–C) Kaplan-Meier curve for RFS based on residual tumor for the cohort of 75 UE patients with re-excision at stage II and stage III (A), 49 UE patients with re-excision at stage II (B), and 26 UE patients with re-excision at stage III (C). (D–F) Kaplan-Meier curve for MFS based on residual tumor for the cohort of 75 UE patients with re-excision at stage II and stage III (D), 49 UE patients with re-excision at stage II (E), and 26 UE patients with re-excision at stage III (F). (G–I) Kaplan-Meier curve for CSS based on residual tumor for the cohort of 75 UE patients with re-excision at stage II and stage III (G), 49 UE patients with re-excision at stage II (H), and 26 UE patients with re-excision at stage III (I).

($P = 0.016$), and CSS ($P = 0.048$). Residual tumors were widely considered a risk predictor for survival [22,23]. We further analyzed the prognostic effect of residual tumors of SS patients stratified according to the AJCC stage. There was a trend for longer RFS in patients without residual tumors at each stage, although no statistical differences were detected. However, a remarkable relationship between residual tumors and MFS ($P < 0.001$) or residual tumors and CSS ($P < 0.001$), was observed at stage II but not stage III, indicating primary wide excision may be more significant for patients at stage II rather than stage III. In addition, the multivariate analysis revealed that UE with residual tumor was an independent risk predictor for RFS, MFS, and CSS, and high grade was another independent factor associated with worse RFS and CSS. This could partially explain that residual tumor may represent the aggressiveness and infiltration of tumor and not exclusively depend on the incomplete local resection.

There were two main changes in the 8th edition of the AJCC staging manual [24]. First, a new tumor size-based T-stage classification rule was applied. Second, tumor depth was no longer included. Additionally, STSs with lymph node metastasis were classified as stage IV diseases. A previous SEER-based large-sample study reported no progress in predictions compared to the 7th edition of AJCC [25]. The study also found that tumor depth was an independent predictive variable that influenced survival, and the 8th edition of the AJCC staging system was poorer compared to the modified staging scheme incorporating tumor depth [25]. Moreover, tumor depth and worse survival remained clinically relevant following the adjustment for tumor size and grade [26–29]. Our study found that tumor depth was an independent predictive variable for RFS, MFS, and CSS, which may support the predictive accuracy of AJCC 7th on patient outcomes.

5. Conclusion

The present study summarizes the clinical features, treatment patterns, and survival-associated factors of patients with SS. Because of the characteristic of soft tissue masses, fine needle aspiration biopsy was strongly recommended if the tumor was highly suspected to be malignant based on imaging and examination, which may lead to adequate primary surgical treatment with more favorable clinical outcomes, especially for those in the early stage. Re-excision after unplanned excision is essential for SS patients to have better outcomes and evaluate the prognosis.

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Ethics approval statement

This investigation was accepted by the Ethics Committee of National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (NCC2020C-341), and complied with the Declaration of Helsinki. The patients in the validation cohort signed their written agreement.

Data availability statement

The authors do not have permission to share data.

CRediT authorship contribution statement

Jin Yuan: Writing - review & editing, Writing - original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Xiaoyang Li:** Writing - review & editing, Supervision, Funding acquisition, Data curation, Conceptualization. **Shengji Yu:** Writing - review & editing, Validation, Supervision, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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