RESEARCH ARTICLE

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Time to Treatment Initiation Analysis in Patients with Localized Extremity Non-Small Round Cell Sarcoma

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Abstract

Introduction: Time-to-treatment initiation (TTI) is an increasingly recognized factor influencing survival in cancer care. Although prolonged TTI has been associated with worse survival in various malignancies, its impact on patients with localized extremity non-small-round-cell sarcoma (NSRCS) remains unclear. **Methods:** Data were extracted from the SEER database, encompassing 11,380 patients diagnosed with localized extremity NSRCS from 2000 to 2019. Patients were categorized into three cohorts based on TTI: less than 1 month, less than 2 months, and less than 4 months. Kaplan-Meier survival analysis and Cox proportional hazards models were used to evaluate the association between TTI and overall survival (OS), adjusting for variables including age, sex, ethnicity, socioeconomic status, tumor location, AJCC stage, and treatment modalities. **Results:** Multivariate analysis revealed that overall survival (OS) in the TTI delay group was nearly equivalent to that of patients with a TTI of less than 1 month (HR = 1.01; 95% confidence interval [CI], 0.97–1.10). In contrast, in cohorts 2 and 3, the TTI delay group demonstrated worse OS (cohort 2: HR = 1.10; 95% CI, 1.02–1.20; cohort 3: HR = 1.30; 95% CI, 1.10–1.70). Subgroup analysis indicated that adjuvant therapy, including chemotherapy and radiation therapy, may potentially mitigate the decreased survival associated with TTI delay. **Discussion:** This study highlights the detrimental impact of delayed TTI on survival in patients with localized extremity NSRCS. Furthermore, it suggests that adjuvant therapy may help mitigate the adverse effects associated with TTI delay.

Keywords: Soft tissue sarcoma- SEER program- Neoplasm grading- Retrospective study- Treatment outcome

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Introduction

Soft tissue sarcomas (STSs) encompass a heterogeneous group of malignancies with a wide range of histological subtypes that can arise in any part of the body [1-3]. These tumors constitute approximately 1% of all cancers and are characterized by their diverse presentations and unpredictable clinical behavior. The rarity and complexity of STSs pose distinct challenges in diagnosis and treatment, requiring specialized expertise and care.

Surgical resection with the goal of achieving clear margins is the cornerstone of treatment for localized STSs [4, 5]. However, the anatomical location of these tumors can complicate surgical intervention, particularly when they are near critical structures. Limb-sparing surgery, which focuses on removing the tumor while preserving the limb, has become a preferred option in many cases. Although this approach offers significant benefits, it is not always feasible, and the decision between limb preservation and amputation must consider various factors, such as tumor size and location [6, 7]. As a result, these complexities can sometimes contribute to delays in initiating treatment for patients with localized extremity STSs.

In recent years, the impact of the time to treatment initiation (TTI) on cancer care has gained increasing attention. TTI for solid tumors has been reported to be 33 days, with shorter TTI observed in colorectal cancer, head and neck cancer, and younger patients, while longer TTI has been reported in older patients and those with lung cancer [8]. Analyses using the National Cancer Database (NCDB) have shown that prolonged TTI is associated with decreased survival; however, the details regarding TTI in STSs remain unclear [9].

To date, population-based cohort studies have begun to shed light on the clinical characteristics and treatment patterns of soft tissue sarcoma, a rare cancer [10-12]. Based on previous reports, we hypothesized that a prolonged TTI

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might be associated with decreased survival. The aim of this study was to investigate the impact of prolonged TTI on survival using a population-based cohort.

Materials and Methods

Patient population

The SEER database comprises 18 cancer registries and covers approximately 28% of the total population of the United States. We used SEER*Stat version 8.4.3 software (National Cancer Institute, Bethesda, MD) to extract data. All cases of extremity STSs diagnosed between 2000 and 2019 were included, as classified by the Rare Cancer classification recode (203) developed by the Surveillance of Rare Cancers in Europe [13]. Primary sites were limited to an extremity according to ICD-O coding (C40.0, 40.3, C40.8, C40.9, C44.6, C44.7, C47.1, C47.2, C49.1, C49.2). A total of 24,605 patients with STSs were initially identified from the SEER database. After excluding cases with unknown cause of death (180 cases), metastatic lesions (1,830 cases), unknown stage (4,917 cases), or lymph node metastatic lesions (179 cases), 17,499 patients were identified as having localized STSs. Of those, unknown histological grade (3992 cases) and unknown T stage (1552 cases) according to the 8th edition of the American Joint Committee on Cancer (AJCC) staging system [14] were excluded. Finally, small round cell sarcoma (370 cases) and unknown months from diagnosis (205 cases) were excluded. In total, 11380 patients were thus included in this study (Figure. 1).

Histological Grading and Classification

The SEER database utilizes an original histological grading system, which we converted to Federation Nationale des Centres de Lutte le Cancer (FNCLCC) grades [15], following previous reports: FNCLCC Grade 1 corresponds to SEER Grade 1, FNCLCC Grade 2 to SEER Grade 2, and FNCLCC Grade 3 to SEER Grade 3. SEER Grade 1 was classified as low grade, while SEER Grades 2–4 were considered high grade [16-18].

Time to Treatment Initiation (TTI)

TTI was defined as the time in months from the diagnosis to the initiation of treatment was determined by calculating the difference between the total number of months from the beginning of the year of diagnosis to the month of diagnosis and the total number of months from the beginning of the year when treatment was initiated to the month when treatment began. We conducted an analysis by establishing three cohorts based on the TTI: Cohort 1; less than 1 month vs 1 month or more, Cohort 2; less than 2 months vs 2 months or more, and Cohort 3; less than 4 months vs 4 months or more.

Statistical analysis

The primary objective of this study was to determine whether TTI impacts survival in patients with non-small round cell sarcomas of the extremities. The secondary objective was to investigate the impact of TTI on survival according to AJCC stage. Overall survival (OS) was estimated using Kaplan-Meier survival analysis. Cox proportional hazards modeling was then employed to calculate hazard ratios (HRs), adjusting for patient characteristics such as age (<15, 15-39, 40-64, >65), sex, ethnicity, socioeconomic status, laterality, primary site, American Joint Committee on Cancer (AJCC) stage, radiation, chemotherapy, and surgical intervention. County-level median household income (inflation-adjusted to 2019 dollars) was used as a proxy for socioeconomic status. Based on the distribution of the study cohort, patients were stratified into three income groups: low (< $50,000), middle ($50,000–$74,999), and high (≥ $75,000). All data were analyzed using JMP Pro version 17.0.0 statistical software (SAS Institute, Cary, NC).

Results

Patient Characteristics

Among the 11,380 patients included in the analysis, TTI delay was observed in 5,294 patients (47%) for 1 month or more, 1,955 patients (17%) for 2 months or more, and 272 patients (2%) for 4 months or more. The TTI delay group had a higher proportion of tumors located in the lower extremities, a higher AJCC stage, and was less likely to receive surgical resection. Regarding adjuvant therapy, TTI delay group had a higher proportion of patients receiving radiation and chemotherapy in cohorts 1 and 2, but the proportions were similar in cohort 3 (Table 1). Regarding socioeconomic status, the distribution of patients across low, middle, and high household income groups is detailed in Table 1.

Survival Analysis

In cohort 1, the 5-year OS was 85% in patients with a TTI of less than 1 month, whereas the 5-year OS in the

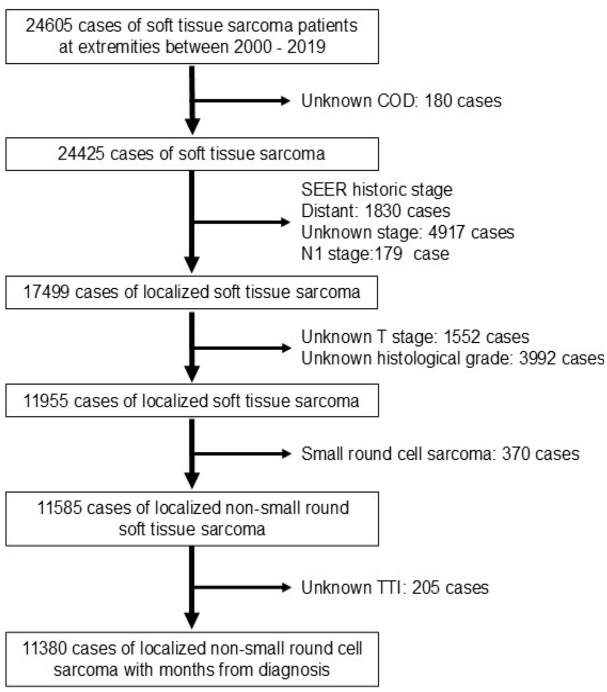

Figure 1. A Flowchart Visually Illustrates the Step-by-Step Process Used to Include Patients in This Cohort

Table 1. Characteristics of Patients in the Study Cohort

		Cohort 1			Cohort 2			Cohort 3		
	All data	0	1+	P value	0-1	2+	P value	0-3	4+(M)	P value
Number	11380	6086 (53%)	5294 (47%)		9425 (83%)	1955 (17%)		11108 (98%)	272 (2%)	
Survival months (M)	68	75	59		71	55		68	53	
Age (categorized, y)				0.01			0.03			0.39
0-14	181 (2%)	112 (2%)	69 (1%)		160 (2%)	21 (1%)		179 (2%)	2 (1%)	
15-39	1554 (14%)	886 (14%)	688 (13%)		1308 (14%)	246 (13%)		1516 (14%)	38 (14%)	
40-64	4745 (42%)	2546 (42%)	2199 (42%)		3941 (42%)	804 (41%)		4621 (42%)	124 (46%)	
65-	4900 (43%)	2562 (42%)	2338 (44%)		4016 (43%)	884 (45%)		4792 (43%)	108 (40%)	
Sex				0.71			0.01			0.9998
Male	6234 (55%)	3324 (55%)	2910 (55%)		5217 (55%)	1017 (52%)		6085 (55%)	149 (55%)	
Female	5146 (45%)	2762 (45%)	2384 (45%)		4208 (45%)	938 (48%)		5023 (45%)	123 (45%)	
Ethnicity				0.01			0.0003			0.25
White	9175 (81%)	4950 (81%)	4225 (80%)		7661 (81%)	1514 (77%)		8966 (81%)	209 (77%)	
Black	1105 (10%)	563 (9%)	542 (10%)		865 (9%)	240 (12%)		1072 (10%)	33 (12%)	
American Indian/ Alaska Native	87 (1%)	54 (1%)	33 (0.6%)		75 (1%)	12 (1%)		85 (1%)	2 (1%)	
Asian or Pacific Islander	941 (8%)	472 (8%)	469 (9%)		766 (8%)	175 (9%)		917 (8%)	24 (9%)	
Unknown	72 (1%)	47 (1%)	25 (0.5%)		58 (1%)	14 (1%)		68 (1%)	4 (1%)	
Median Household Income										
Low income	1270 (11%)	702 (12%)	568 (11%)	0.13	1065 (11%)	205 (10%)	0.23	1245 (11%)	25 (9%)	0.13
Middle income	6432 (57%)	3389 (56%)	3043 (57%)		5294 (56%)	1138 (58%)		6262 (56%)	170 (63%)	
High income	3678 (32%)	1995 (33%)	1683 (32%)		3066 (33%)	612 (31%)		3601 (32%)	77 (28%)	
Laterality				0.48			0.18			0.84
Right	5680 (50%)	3069 (50%)	2611 (49%)		4730 (50%)	950 (49%)		5548 (50%)	132 (49%)	
Left	5695 (50%)	3014 (50%)	2681 (51%)		4692 (50%)	1003 (51%)		5555 (50%)	140 (51%)	
Unknown	5 (0.04%)	3 (0.05%)	2 (0.04%)		3 (0.03%)	2 (0.1%)		5 (0.05%)	0 (0%)	
Primary site				<.0001			<.0001			0.06
Upper	2809 (25%)	1695 (28%)	1114 (21%)		2395 (25%)	414 (21%)		2755 (25%)	54 (20%)	
Lower	8571 (75%)	4391 (72%)	4180 (79%)		7030 (75%)	1541 (79%)		8353 (75%)	218 (80%)	
Histology				<.0001			<.0001			0.18
Myxofibrosarcoma	1271 (11%)	719 (12%)	552 (10%)		1068 (11%)	203 (10%)		1241 (11%)	30 (11%)	
histiocytoma	1111 (10%)	636 (10%)	475 (9%)		983 (10%)	128 (7%)		1092 (10%)	19 (7%)	
Other fibromatous neoplasms	295 (3%)	188 (3%)	107 (2%)		246 (3%)	49 (3%)		288 (3%)	7 (3%)	

Table 1. Continued

		Cohort 1			Cohort 2			Cohort 3		
	All data	0	1+	P value	0-1	2+	P value	0-3	4+(M)	P value
Histology				<.0001			<.0001			0.18
Liposarcoma	3227 (28%)	1875 (31%)	1352 (26%)		2674 (28%)	553 (28%)		3132 (28%)	95 (35%)	
Synovial sarcoma	609 (5%)	291 (5%)	318 (6%)		486 (5%)	123 (6%)		589 (5%)	20 (7%)	
Leiomyosarcoma	1196 (11%)	678 (11%)	518 (10%)		1004 (11%)	192 (10%)		1172 (11%)	24 (9%)	
Spindle cell sarcoma	447 (4%)	213 (4%)	234 (4%)		351 (4%)	96 (5%)		433 (4%)	14 (5%)	
Epithelioid sarcoma	88 (0.8%)	51 (1%)	37 (1%)		72 (1%)	16 (1%)		86 (1%)	2 (1%)	
Giant cell sarcoma	1425 (13%)	601 (10%)	824 (16%)		1146 (12%)	279 (14%)		1400 (13%)	25 (9%)	
Other soft tissue sarcomas	1368 (12%)	649 (11%)	719 (14%)		1108 (12%)	260 (13%)		1339 (12%)	29 (11%)	
Peripheral	159 (1%)	83 (1%)	76 (1%)		134 (1%)	25 (1%)		155 (1%)	4 (1%)	
Other	184 (2%)	102 (2%)	82 (2%)		153 (2%)	31 (2%)		181 (2%)	3 (1%)	
AJCC				<.0001			<.0001			0.0006
1A	634 (6%)	470 (8%)	164 (3%)		564 (6%)	70 (4%)		623 (6%)	11 (4%)	
1B	1805 (16%)	1169 (19%)	636 (12%)		1514 (16%)	291 (15%)		1741 (16%)	64 (24%)	
2	3150 (28%)	2161 (36%)	989 (19%)		2764 (29%)	386 (20%)		3097 (28%)	53 (19%)	
3A	2996 (26%)	1360 (22%)	1636 (31%)		2425 (26%)	571 (29%)		2928 (26%)	68 (25%)	
3B	2795 (25%)	926 (15%)	1869 (35%)		2158 (23%)	637 (33%)		2719 (24%)	76 (28%)	
Radiation				<.0001			<.0001			0.22
Yes	6433 (57%)	2882 (47%)	3551 (67%)		5222 (55%)	1211 (62%)		6292 (57%)	141 (52%)	
No/Unknown	4947 (43%)	3204 (53%)	1743 (33%)		4203 (45%)	744 (38%)		4816 (43%)	131 (48%)	
Chemotherapy				<.0001			0.02			0.73
Yes	1760 (15%)	635 (10%)	1125 (21%)		1423 (15%)	337 (17%)		1720 (15%)	40 (15%)	
No/Unknown	9620 (85%)	5451 (90%)	4169 (79%)		8002 (85%)	1618 (83%)		9388 (85%)	232 (85%)	
Surgery				<.0001			<.0001			0.0007
Performed	11055 (97%)	6041 (99%)	5014 (95%)		9229 (98%)	1826 (93%)		10800 (97%)	255 (94%)	
No/Unknown	325 (3%)	45 (1%)	280 (5%)		196 (2%)	129 (7%)		308 (3%)	17 (6%)	

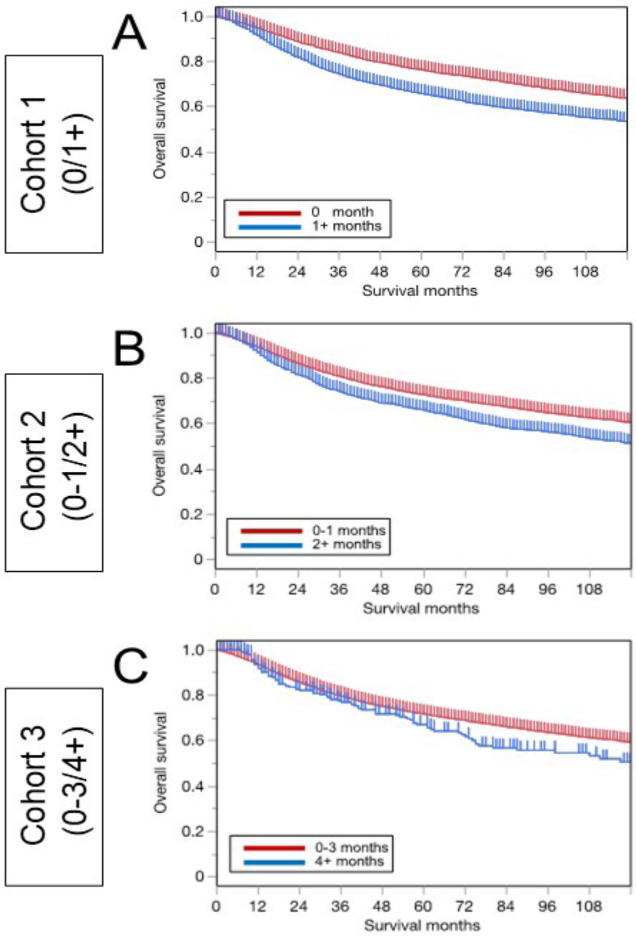

Figure 2. Kaplan-Meier Curves for Overall Survival According to Time to Treatment Initiation (TTI). (A) TTI less than 1 month vs. 1 month or more, (B) TTI less than 2 months vs. 2 months or more, and (C) TTI less than 4 months vs. 4 months or more.

TTI delay group (≥ 1 month) was 66%. In cohort 2, the 5-year OS was 73% in patients with a TTI of less than 1 month, whereas the 5-year OS in the TTI delay group (≥ 2 months) was 66%. In cohort 3, the 5-year OS was 72% in patients with a TTI of less than 3 months, whereas the 5-year OS in the TTI delay group (≥ 4 months) was 67%. In multivariate analysis, OS in the TTI delay group was almost equal to that in patients with a TTI of less than 1 month (HR = 1.0, 95% confidence interval [CI] 0.97-1.1, Figure 2A). In contrast, in cohorts 2 and 3, the TTI delay group showed worse OS (Cohort 2: HR = 1.1, 95% CI 1.02-1.2; Cohort 3: HR = 1.3, 95% CI 1.1-1.7, Figure 2B and 2C).

Subgroup Analysis in patients who received adjuvant therapy

We next investigated whether adjuvant therapy affected survival in patients with TTI delay. Regarding radiation therapy, patients in the group with a TTI delay of 2 months or more who did not receive radiation showed worsened OS (cohort 1: HR = 1.1, 95% CI 0.98-1.2, Figure 3A; cohort 2: HR = 1.2, 95% CI 1.01-1.3, Figure 3B; cohort 3: HR = 1.6, 95% CI 1.2-2.1, Figure 3C). In contrast, the OS in the TTI delay group who received radiation was almost equal to that in the group without TTI delay (cohort 1: HR = 0.9, 95% CI 0.9-1.1, Figure 3D; cohort 2: HR = 1.1, 95% CI 0.96-1.2, Figure 3E; cohort 3: HR = 1.1, 95% CI 0.8-1.5, Figure 3F). Regarding chemotherapy, patients in the TTI delay group who did not receive chemotherapy showed worsened OS (cohort 1: HR = 1.1, 95% CI 0.99-1.2, Figure 4A; cohort 2: HR = 1.1, 95% CI 1.004-1.2, Figure 4B; cohort 3: HR = 1.4, 95% CI 1.1-1.8, Figure 4C). In contrast, the OS in the TTI delay group who received chemotherapy was almost equal to that in the group without TTI delay (cohort 1: HR = 0.9, 95% CI 0.8-1.1, Figure 4D; cohort 2: HR = 1.1, 95% CI 0.9-1.3, Figure 4E; cohort 3: HR = 1.0, 95% CI 0.6-1.6, Figure 4F).

Discussion

This study clearly demonstrated that approximately half of the localized extremity non-small round cell sarcoma experienced TTI delay of one month or more. It also showed that tumors in the lower extremities and those with a higher AJCC stage were more likely to have a prolonged TTI. Furthermore, TTI delay worsened survival in patients with localized extremity soft tissue sarcoma. On the other hand, adjuvant therapy, such as chemotherapy and radiation therapy, was shown to potentially rescue the decreased survival in the TTI delay group.

Regarding previous reports on TTI in soft tissue

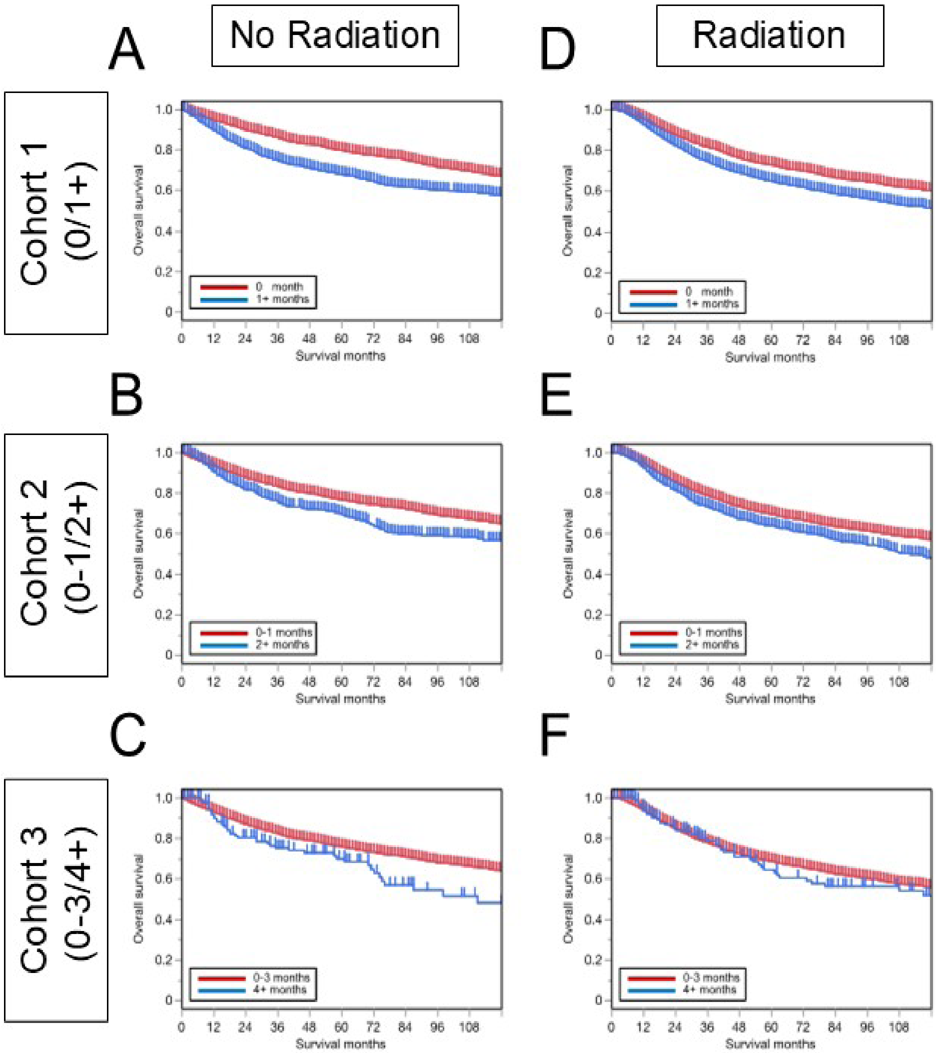

Figure 3. Kaplan-Meier Curves for Overall Survival based on Radiation Therapy. (A-C) Patients who did not receive radiation therapy; (D-F) patients who received radiation therapy. (A and D) TTI less than 1 month vs. 1 month or more; (B and E) TTI less than 2 months vs. 2 months or more; (C and F) TTI less than 4 months vs. 4 months or more.

sarcoma treatment, a study using the Swiss Sarcoma Network on 266 cases of bone and soft tissue tumors found that the median TTI was 30 days, with variations based on the site of origin: 28 days for deep-seated or bone tumors and 42 days for subcutaneous tumors [19]. This suggests that subcutaneous tumors may be underestimated. Additionally, a study of 223 cases of soft tissue sarcoma from the New Zealand sarcoma multidisciplinary meeting reported that a TTI of more than 30 days was associated with worse distant metastasis-free survival [20]. Ogura et al. also reported that in cases of histological high-grade soft tissue sarcoma analyzed using the NCDB, a TTI of more than 30 days was associated with decreased survival [21]. In line with these previous reports, our study demonstrated that patients with a TTI delay of 2 months or more had decreased survival, and furthermore, this negative impact on survival could potentially be rescued by adjuvant therapy.

Another important aspect to consider is the underlying factors contributing to TTI delays. These could include delays in diagnosis, extended time required for treatment decision-making, and patient-related factors such as socioeconomic status [22]. In our study, patients with higher AJCC stages experienced prolonged TTI, suggesting the need for prompt decision-making regarding treatment plans, such as the consideration of adjuvant therapy and coordination when multiple specialties are involved. Understanding these contributing factors is essential for identifying areas where interventions can be made to reduce TTI. Given the significant impact of TTI on survival, efforts should be directed towards streamlining the diagnostic and treatment processes, potentially through multidisciplinary collaboration and early intervention strategies [23]. Moreover, the findings of this study could inform future clinical guidelines, emphasizing the importance of minimizing TTI to improve outcomes for patients with soft tissue sarcoma.

Several limitations should be considered when interpreting our results. First, a limitation inherent to the SEER database is the lack of specific clinical variables. Our study did not account for the reasons behind TTI delay and did not include data on ECOG performance status (PS) [24] or specific comorbidities. This omission suggests that patients in the TTI delay group may have required

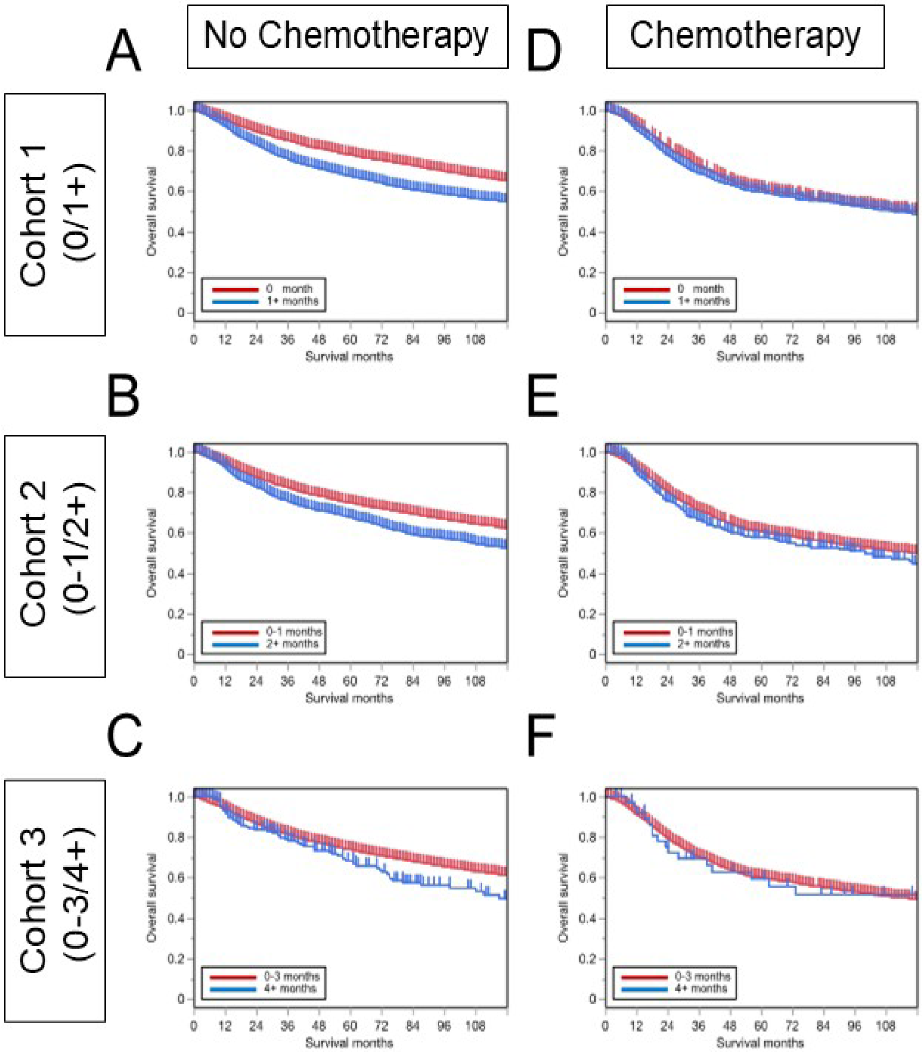

Figure 4. Kaplan-Meier Curves for Overall Survival based on Chemotherapy. (A-C) Patients who did not receive chemotherapy; (D-F) patients who received chemotherapy. (A and D) TTI less than 1 month vs. 1 month or more; (B and E) TTI less than 2 months vs. 2 months or more; (C and F) TTI less than 4 months vs. 4 months or more.

additional time for the assessment of preoperative medical complications that were not captured in the dataset. Consequently, patients with more medical comorbidities and a tendency toward lower PS may have been included in the TTI delay group, introducing some degree of selection bias. Second, the TTI periods examined were measured in months, not days. Since the SEER database records dates only in months and years to ensure patient confidentiality, a granular analysis based on days was not technically feasible. Finally, the SEER database provides only information from the time of diagnosis and its outcomes, so we could not assess changes in clinical stage due to TTI delays. Future prospective studies including these factors are necessary.

In conclusion, this study found that delayed TTI was associated with decreased survival in patients with localized extremity non-small round cell sarcoma, and adjuvant therapy could potentially rescue this decline in survival. While the lack of consideration for ECOG PS and comorbidities warrants caution in interpreting these findings, the use of adjuvant therapy should be considered for patients with unavoidable TTI delays.

Author Contribution Statement

MM was involved in the design of the study, performed the clinical assessment, analysis, and interpretation of data, and drafted and revised the manuscript. ST, TO, and KI assisted with data interpretation and revised the manuscript for important intellectual content. DS, TE, EK, and NI were involved in data acquisition and revised the manuscript critically for important intellectual content. All authors have read and approved the final manuscript.

Acknowledgements

Availability of data

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Ethical approval

In accordance with local legislation and institutional requirements, ethical review and approval were not required for this study. The Surveillance, Epidemiology, and End Results (SEER) database is a publicly available resource that contains de-identified patient data.

Conflict of interest

The authors declare that they have no conflict of interest.

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