Patients with increased time to treatment initiation have poorer survival after definitive surgery for localised high-grade soft tissue sarcoma in the extremity and trunk: Report from the National Cancer Database (NCDB)

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Abstract

AIMS: There is no consensus on impact of time to treatment initiation (TTI) on survival in patients with soft tissue sarcoma (STS). The purpose is to: 1) examine if increased TTI is associated with overall survival (OS), and 2) identify what are the factors associated with the delayed TTI in patients with soft tissue sarcoma.

PATIENTS AND METHODS: We identified 23,786 localised high-grade STS of the extremity and trunk who underwent definitive surgery from 2004–2015 using the National Cancer Database. The Cox proportional hazards model was used to examine the relationship between each factor and OS. We calculated the incidence rate ratio (IRR) using negative binomial regression models to identify factors affecting TTI.

RESULTS: Patients in whom TTI was prolonged had poorer OS than those with TTI of 0–30 days: 31–60 days, HR, 1.08; *P* = 0.011, 61–90 days, HR: 1.11; *P* = 0.044, 91- days, HR: 1.22; *P* = 0.003 (vs. 0–30 days). The restricted cubic spline demonstrated the HR increased substantially longer TTI than 50 days. Non-academic centers (vs. academic centers; IRR = 0.64–0.86; P < 0.001) had shorter TTI, while insurance status of Medicaid (vs. private insurance; IRR = 1.34), uninsured (vs. private insurance; IRR = 1.17), and transition in care (IRR = 1.62) had longer TTI.

CONCLUSION: TTI over 30 days after diagnosis was independently associated with poorer survival. Hazard ratio showed linear increase, especially > 50 days after diagnosis. We recommend initiating treatment within 30 days after diagnosis to achieve the highest likelihood of cure for

localised high-grade STS in the extremity and trunk, even when case referral to a specialised center is required.

INTRODUCTION

The interval from diagnosis to the time to treatment initiation (TTI) is increasing in the United States (US) in cancer patients[1]. The cause of increased TTI includes patient factors, socioeconomic factors, or health care system such as more complicated diagnostic and therapeutic techniques or increasing transitions in care to specialised hospitals. For physicians to reassure patients that current wait times to initiate treatment do not impact long-term outcomes to eliminate patient anxiety and distress associated with delays in TTI, there should be evidence that the length of TTI does not affect the outcome. Although studies in breast, head and neck, gynecologic, and lung cancer suggest that increased TTI is associated with poor survival[2–7], the evidence is conflicting in most cancer types. Moreover, it is still unclear if delayed TTI worsens the outcomes of patients with soft tissue sarcoma[8, 9].

Soft-tissue sarcomas are heterogeneous neoplasms originating from mesenchymal cells, comprising more than 70 histological subtypes. In high grade soft tissue sarcomas, the tumour grows rapidly and has the potential risk of micro-metastases that cannot be detected by imaging in cases with increased TTI. In addition to this biological background, the rarity and heterogeneity of soft tissue sarcomas inevitably hinders accurate diagnosis and sometimes demands long TTI. Therefore, we hypothesize increased TTI is associated with poor survival in soft tissue sarcoma. However, there have been no reports analysing the impact of TTI on survival in patients with localised high-grade soft tissue sarcoma of the extremity and trunk treated with definitive surgery.

We focused on localised high-grade soft tissue sarcoma of the extremity and trunk treated with definitive surgery and aimed to: 1) examine if the increased TTI is associated with the overall survival (OS), and 2) identify what are the factors influencing the delayed TTI by analysing data from the National Cancer Database (NCDB).

PATIENTS, MATERIALS, AND METHODS

NCDB

The NCDB is a national hospital-based cancer registry jointly sponsored by the American College of Surgeons and the American Cancer Society. Although submissions of patient records to the NCDB were voluntary and open to all cancer facilities in the US, data collection was mandated as a requirement of the Commission on Cancer approved programs since 1997. Currently, NCDB data represent more than 70% of newly diagnosed cancer cases in the US. This study is a STROBE-compliant retrospective study. Due to the

anonymous nature of the data, informed consent was waived, and institutional review board approval was not required for this study.

Data extraction

Patients eligible for study inclusion had high-grade, non-metastatic adult soft tissue sarcoma of the extremity or trunk treated with definitive surgery. First, cases of bone and soft tissue sarcoma diagnosed from 2004–2015 were extracted from the NCDB using the International Classification of Diseases-Oncology, Third Edition (ICD-O-3) topography codes (40.x, C41.x, C47.x, C48.x, and C49.x) (n = 136,144). As in the previous reports analysing TTI using NCDB[1, 5, 6, 8, 9], TTI was defined as the time from histologic diagnosis of malignancy to initiation of first definitive treatment. Initiation of first definitive treatment is surgery in most of the cases. However, if patients receive preoperative chemotherapy or radiotherapy, initiation of first definitive treatment was defined as the first day of chemotherapy or radiotherapy. Patients with TTI >365 days were excluded because of concerns surrounding miscoding. Inclusion and other exclusion criteria are summarised in Figure 1. We excluded ineligible patients, and the final cohort was composed of 23,786 patients.

For each patient, we extracted the following data: sex, age (<65 and 65 years of age), race, insurance status (private insurance, Medicaid, Medicare, other government, uninsured), zip-code level income, zip-code level education, Charlson/Deyo comorbidity scores, tumour location, histological grade, American Joint Committee on Cancer (AJCC) stage, and facility type. Race was categorised into White, Black, Asian, and others, including Pacific Islanders and Native Americans. Type of treatment facility was categorised into community, comprehensive community, academic/research program (includes National Cancer Institute-designated Comprehensive Cancer Centers), or others. Charlson/Deyo comorbidity scores were categorised into 0 (no comorbid conditions reported), 1, or 2 (> 1 comorbid condition reported). Income level was categorised as quartiles based on equally proportioned income ranges among all US zip codes. Education level was defined as the estimated number of adults in a patient's zip code who did not graduate from high school and is categorised as equally proportioned quartiles among all US zip codes. Histologic grade was categorised into 2 (moderately differentiated), 3 (poorly differentiated), and 4 (undifferentiated). As different AJCC stage editions (sixth and seventh) were used in our dataset, we converted stage from the sixth to seventh as appropriate. These were categorised into stage 2 or 3. The transition in care was defined as a change in facility type from diagnosis to definitive treatment. We categorised TTI into four prespecified groups: 0–30 days, 31–60 days, 61–90 days, and 90– days.

Endpoints

The primary endpoint was OS, which was defined as the period from the date of diagnosis and the date on which the patient was last contacted or died. The secondary endpoints were 30-day and 90-day mortality, which was defined as death 30 or fewer and 90 or fewer days after surgery.

Statistical Analyses

We performed univariate comparisons of proportions using the chi-square test and comparisons of averages using analyses of variance. The OS was estimated using the Kaplan-Meier method, and comparisons were assessed using the log-rank test. Univariate and multivariate analyses were conducted using the Cox proportional hazards model. The TTI was entered into the Cox regression model by using a restricted cubic spline to allow for a nonlinear relationship between TTI and hazard ratio. The model was optimised by testing splines constrained by 3–7 knots, and final model selection was based on the Akaike Information Criteria (AIC) [5, 10]. Logistic regression analyses were performed to examine the relationships of each factor with the 30-day and 90-day mortality.

As one of our goals was to determine what factors influenced the TTI, we calculated the incidence rate ratio (IRR) by multivariate analysis using negative binomial regression models, containing all covariates to control for confounders. IRR is defined that for every 1-point increase in the independent variable while holding all other variables in the model constant, the TTI rate (in days) would increase by a factor of that value.

Differences were considered to be statistically significant at $P < 0.05$. All statistical analyses were conducted using IBM SPSS version 23.0 (IBM SPSS, Armonk, NY, USA) and R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Demographics

We identified 23,786 eligible patients from 2004–2015. Details of histologic diagnosis and background characteristics of patients according to 30-day interval TTI are shown in Table 1 and Appendix 1. Median and mean TTI was 14.0 days (interquartile range [IQR], 0–32 days) and 20.9 days (standard deviation [SD], 27.5 days), respectively. Median TTI had increased significantly over the year ($P < 0.001$) (Figure 2). TTI varied significantly according to socioeconomic status, including race, insurance status, income, and education, as well as patient and tumour factors including age, Charlson Deyo score, tumour location/grade, and AJCC stage. Of these, facility type, insurance status, and AJCC stage had the largest difference when compared to each group by median TTI.

Impact of TTI on OS and short-term mortality

Figure 3 (left panel) shows the Kaplan–Meier plots for OS stratified by TTI. The five-year OS were 57.7%, 53.9%, 50.6%, and 49.9% in TTI of 0–30 days, 31–60 days, 61–90 days, and 91– days, respectively (log-rank test, $P < 0.001$). The follow-up rates at 5- and 10-years were 67% and 48%, respectively.

Table 2 shows the unadjusted and adjusted hazard ratios obtained from the Cox proportional hazards models for OS. Prolonged TTI was significantly associated with poorer OS compared to TTI of 0–30 days (31–60 days, hazard ratio [HR], 1.08; 95% confidence interval [CI], 1.02–1.14; $P = 0.011$, 61–90 days, HR: 1.11; 95% CI, 1.00–1.22; $P = 0.044$, 91– days, HR: 1.22; 95% CI, 1.07–1.39; $P = 0.003$). Among patient factors, sex ($P < 0.001$),

age (P <0.001), and Charlson/Deyo score (P < 0.001) were significantly associated with OS. Among socioeconomic factors, insurance status, income level, and education level were significantly associated with OS. Tumour or surgical factors, including tumour location (P < 0.001), histologic grade (P < 0.001), AJCC stage (P < 0.001), and surgical margin (P <0.001) were significant predictors for OS. Survival curves according to TTI after adjusting for other confounders using Cox regression model (Figure 3 [right panel]) demonstrated there were clinically meaningful differences in OS.

HR of OS adjusted for all covariates according to TTI as a continuous variable by using restricted cubic splines with 5 knots was shown in Figure 4. We found that the HR of death concerning a TTI of zero is the lowest and there is a tendency of increasing HR with TTI being >50 days. Considering substantially increased HR with a TTI > 50 days, we should initiate treatment within 50 days of diagnosis.

Data on 30- and 90-day mortality was available in 98.7% (23,465/23,786) and 97.8% (23,260/23,786) of the study population, and these cases were included in the logistic regression analysis to investigate the relationship between short-term mortality and each factor including TTI. Overall short-term mortality was 0.7% and 2.5% at 30-days and 90-days postoperatively, respectively. Multivariate logistic regression analyses did not show significant associations between 30- and 90-day mortality and TTI although some important factors affecting short-term mortality were identified including age, Charlson/Deyo score, tumour location, AJCC stage, and surgical margin (Appendix 2).

Factors affecting TTI

IRRs by multivariate analysis using negative binomial regression models were computed to identify factors affecting TTI (Table 3). Because of high statistical power, all the variables except age were significantly associated with TTI. Of these, facility type, insurance status, AJCC stage, and transition in care had the greatest impact on TTI. Regarding facility type, academic hospital had significantly increased TTI with IRR of other facility types ranging 0.64–0.86. Increased TTI was found in patients with Medicaid (IRR = 1.34; P < 0.001) and those who were uninsured (IRR = 1.17; P < 0.001). Patients with AJCC stage 3 tumour had increased TTI compared to those with stage 2 (IRR = 1.29; P < 0.001). Patients experiencing a transition in care had the greatest increase in TTI (IRR = 1.62; P < 0.001).

DISCUSSION

The relationship between TTI and outcomes is of current interest, as TTI has increased in the past decade as was shown in our analysis (Figure 2). This could be due to reasons to pursuit better care[6], including advances in pretreatment evaluations such as FDG-PET[11, 12], and second opinion or transition in care to specialised centers[1, 6, 8]. Although TTI is shown as a factor to be considered when treating patients in various cancers including breast[2, 3], lung[4, 7], and head and neck cancers[5, 6], information on TTI and its impact on survival in patients with soft tissue sarcoma is limited[8, 9].

Curtis et al.[8] analysed TTI and influential factors for TTI using 41,592 patients with AJCC stage 1–4 soft tissue sarcoma of the head and neck, extremity, and trunk treated by any

treatment modality including palliative surgery and non-surgical treatment. They reported median TTI was 22 days, and transition in care had the greatest impact on increased TTI[8]. Featherall et al.[9] analysed the impact of TTI on OS using 8,648 patients with high-grade soft tissue sarcoma of the head and neck, extremity, and trunk treated by any treatment modality including palliative surgery and non-surgical treatment (13%). Based on their analyses[9], there was little to no clinically relevant association of longer TTI with poor survival in contrast to what was observed in other cancer types[2–7]. However, there have been no reports analysing the impact of TTI on OS in patients with high-grade soft tissue sarcoma of the extremity and trunk treated by definitive surgery. Therefore, we have had no information on what TTI is acceptable to cure this disease. In the present study, median TTI in overall patients was 14 days, which is much shorter than those in previous reports (22 days)[8]. This is likely because only patients treated with curative intent by definitive surgery were included. The factor that had the greatest impact on increased TTI was a transition in care, which was concordant with the previous study[8]. We also found facility type, insurance status, and AJCC stage had major impact on TTI. Increased TTI in the academic centers can be explained by the fact that soft tissue sarcoma is rare cancer and usually referred to predominately academic centers.

In contrast to the report by Featherall et al.[9], we demonstrated that TTI was associated with OS, and survival difference was evident (Figure 3 and Figure 4). These conflicting conclusions may result from the difference in eligibility. We only included patients treated with curative intent by definitive surgery and excluded patients with soft tissue sarcoma arising in the head and neck where treatment strategy and outcomes are different due to anatomic constraints, leading to difficulty in completely excising tumours with high rates of local recurrence.

Insurance status had a great impact both on prolonged TTI and OS. Given insurance status is considered to directly influence access to health services, its effects to the TTI and OS seems reasonable. Improved insurance reforms, such as Medicaid expansion to nonelderly adults with low incomes in selected states conducted by the Affordable Care Act might improve TTI, as well as OS through better access to health care. As expected, the report analysing the effect of Medicaid expansion on cancer care demonstrated it was associated with a decreased rate of uninsured patients and an increased rate of early-stage cancer diagnosis [13]. In the Sarcoma Policy Checklist in Europe, which provides policymakers with priority areas to improve care for sarcoma patients, one of the recommendations is sarcoma patients should have more rapid access to effective treatments[14]. However, there has not been concrete and quantitative evidence to support this recommendation. We believe our findings reinforce the need of creating the medical care system for STS patients to access to appropriate care in an efficient way.

Notably, the concept and policy of structured referral to specialty centers for high impact rare diseases is standard in the UK and Europe, whereas it is not so widely accepted in the US. Although perverse financial motives and conflicts of interest underly the largely private US system, our findings have the potential to alter the perspective of US physicians and health care systems, and it serves as an affirmation of the UK and European approach. Indeed, the establishment of the National Institute for Health and Care Excellence (NICE)

criteria in 2006 for referral of soft tissue masses within two weeks has contributed to the reduction in size of soft tissue sarcomas treated in the UK and improved results[15]. We hope that similar improvements can be achieved in the US, and critical review of the NCDB data will promote this.

Our study has several limitations. First, database study usually has incomplete or inaccurate data, that can bias the results. There may be an underestimation or overestimation of comorbidities or outcomes due to incomplete reporting. Second, we cannot determine if patient death is cancer-specific or not, as the NCDB does not include the cause of death. Therefore, the relationship between each factor, including TTI and disease-specific survival for soft tissue sarcoma patients, is unknown. Also, the database relies on abstractors to determine whether surgery was performed for curative intent; therefore, it is not known if R2 resected tumours were for curative or palliative intent. Third, the participation rate of small hospitals in the NCDB was relatively low. Hospitals participating in the NCDB represents the American College of Surgeons Commission on Cancer accredited hospitals and does not reflect all inpatient hospitals in the US; this may have resulted in a sample selection bias. Fourth, we may not be able to determine deaths after transfer to another hospital, which may have resulted in an underestimation of outcomes. Fifth, we were not able to identify several important clinical parameters that may have affected the OS, including the severity of preoperative comorbidities, response to chemotherapy, and details of surgery. Sixth, we could not detect the patients' contribution to treatment delay, or the influence of symptoms-to-treatment interval on OS. Increased TTI is composed of two factors: 1) time from a patient's first awareness of symptoms to diagnosis (predominantly patient-related), and 2) time from a patient's first histologic diagnosis to treatment (predominantly physician- or hospital-related). We only focused on physician- or hospital-related TTI because patient-related TTI is not recorded in the NCDB. Additional investigation considering patient-related TTI is warranted to draw a more nuanced statement regarding the effect of TTI on survival in soft tissue sarcoma. Finally, it is possible that undefined comorbid factors could contribute to the delay and affect patient survival. The association of soft tissue doubling time with survival has been reported to be within the relevant span reported in this study (median 26 days; mean 57 days)[16]. The limited number of factors included in the database preclude testing most potential hypotheses. In addition to reducing patient survival, treatment delays may have other effects such as increased malpractice claims and payments[17].

The implications and application of these findings may differ in other medical systems based on insurance system, prevailing patient referral patterns, and the established regionalization of care. For example, significant comorbidity and referral to specialised centers are universal factors affecting longer TTI in many countries and in the US. The prevailing policy guidelines and medical culture influence results as seen in the reduced size and improved outcome of UK soft tissue sarcoma patients since the 2006 NICE criteria mandate for prompt referral to specialized centers. Our finding that insurance was one of the greatest factors affecting delayed treatment initiation cannot be applied to countries that have different insurance systems. New modes of medical care, such as Telemedicine, may help reduce the delays and mitigate these effects regardless of the medical system.

In conclusion, we demonstrated that TTI had a significant impact on OS, but not on short-term mortality, in patients with localised high-grade soft tissue sarcoma in the extremity and trunk treated with definitive surgery. Although differences in patient background characteristics among the groups may have affected outcomes, we identified an independent association between TTI and OS after adjusting for these confounders. We recommend arranging to initiate treatment within 30 days after diagnosis to aim for the cure of localised high-grade soft tissue sarcoma in the extremity and trunk, even though referral to a specialised center is required.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TAKE HOME MESSAGE

- Increased time to treatment initiation is associated with poorer overall survival in patients with soft tissue sarcoma.

- We recommend initiating treatment within 30 days after diagnosis to achieve the highest likelihood of cure for localised high-grade soft tissue sarcoma in the extremity and trunk, even when case referral to a specialised center is required.

Patients with bone and soft tissue sarcoma diagnosed from 2004 to 2015 in the NCDB using the site and histology codes (n = 136,144).

Excluded:
- Bone sarcoma, not STS histology, benign/intermediate soft tissue tumour (n = 48,562)
- Low grade (n = 8,204)
- Tumour arising from other than extremity or trunk: head, face, neck, and heart etc. (n=12,216)
- Distant metastasis at diagnosis present or unknown (n=3,522)
- No definitive surgery (n = 22,226)
- Overall survival data missing (n = 10,218)
- Age < 15 years (n = 1,357)
- TTI* data missing or TTI >365 days (n = 4,120)
- Other miscellaneous reasons (n = 1,933)

Eligibility: High grade, non-metastatic STS of the extremity or trunk treated with definitive surgery (n = 23,786)

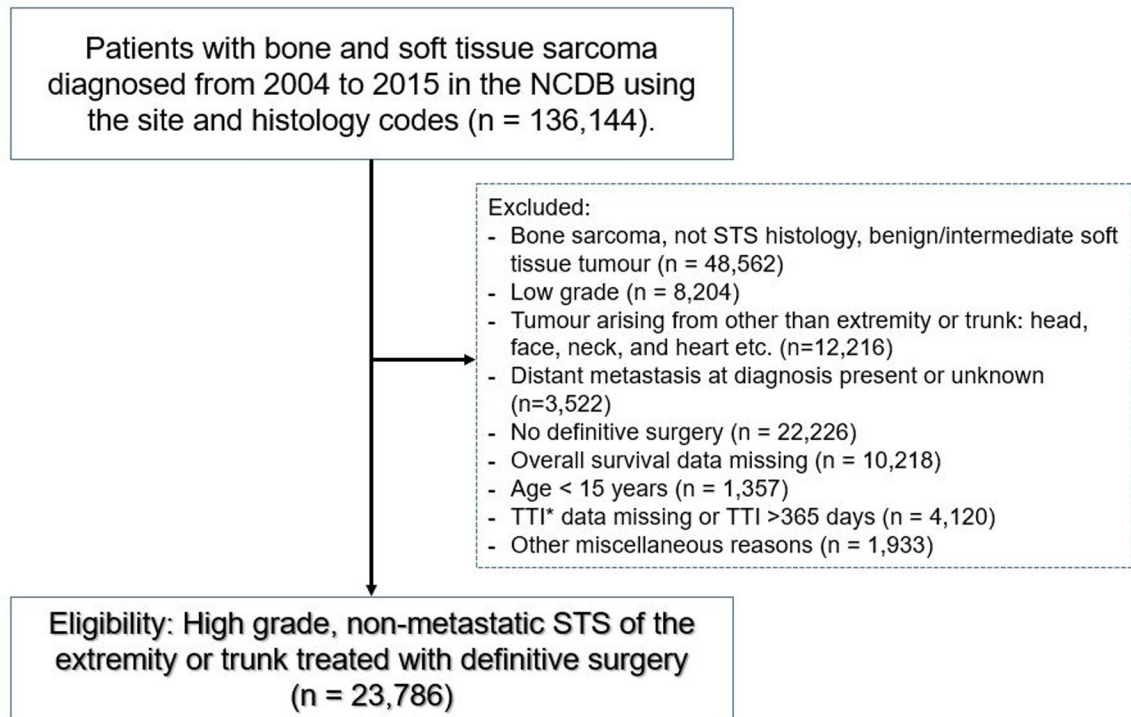**Figure 1.**

Flow diagram of the study. NCDB = National Cancer Database; STS = soft tissue sarcoma; TTI = time to treatment initiation.
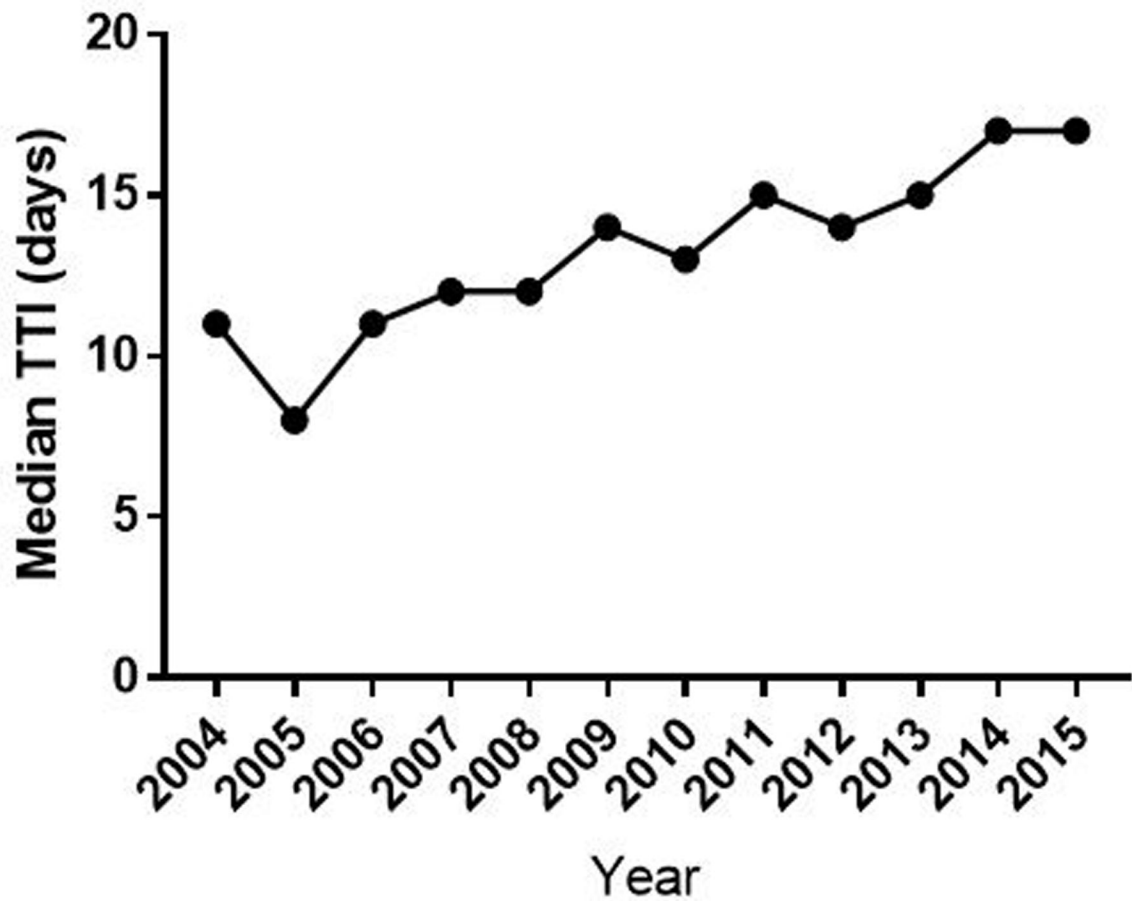
Figure 2.
Median TTI by year of diagnosis. TTI = time to treatment initiation.

TTI (days	5 year survival	10 year survival
0-30	57.7%	42.4%
31-60	53.9%	37.2%
61-90	50.6%	34.1%
91-	49.9%	31.4%
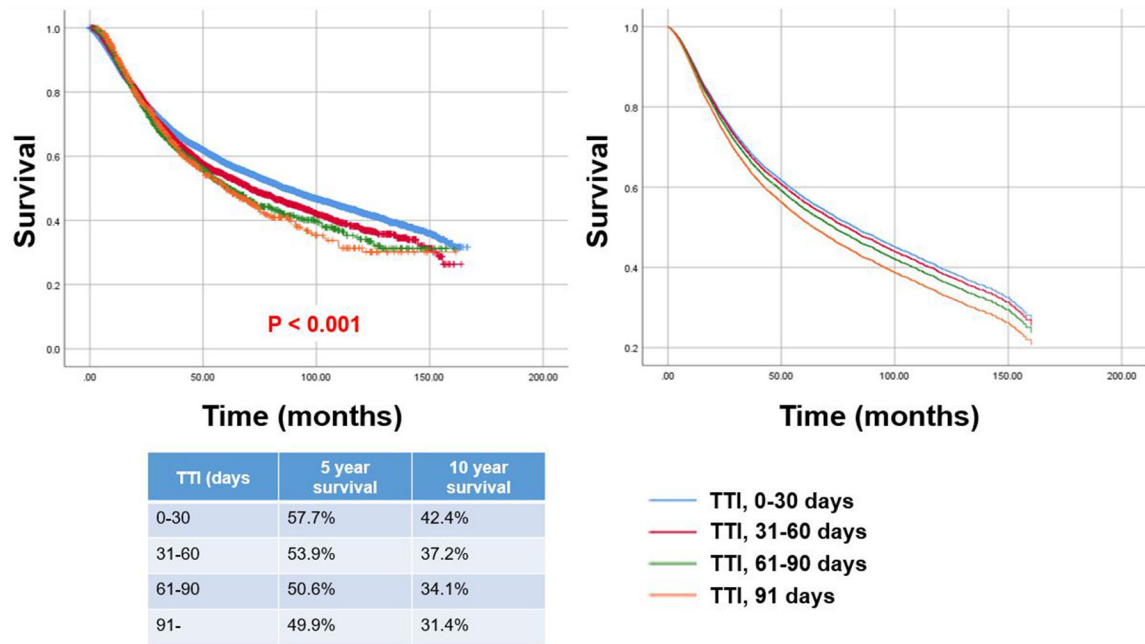
Figure 3.

Kaplan-Meier plots of <u>overall survival</u> (<u>OS</u>) for all patients stratified by prespecified TTI groups: 0–30 days, 31–60 days, 61–90 days, and 90– days (left panel) (univariate comparison, log-rank test, *P* < 0.001). Survival curves according to prespecified time to treatment initiation groups after adjusting for other confounders using Cox regression model (right panel). <u>OS</u> = overall survival; TTI = time to treatment initiation.

RCS (adjusted hazard ratio)
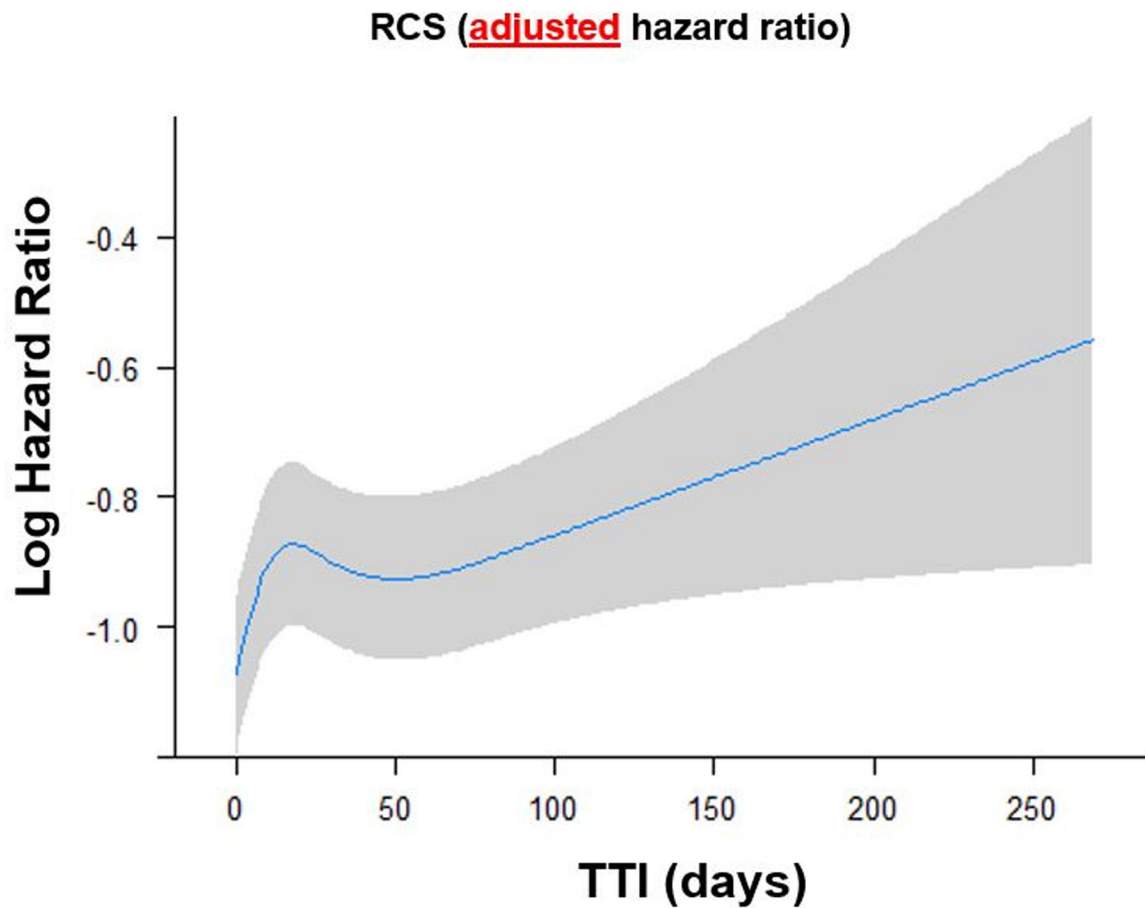
Figure 4.
Adjusted HR of overall survival (OS) according to time to treatment initiation (TTI) as a continuous variable by using restricted cubic splines with five knots. The restricted cubic spline allows for a nonlinear relationship of TTI with the log HR of OS after adjusting for other confounders, estimated from the Cox regression model. With a TTI > 50 days, the HR increased substantially. OS = overall survival; TTI = time to treatment initiation.

Table 1.

Details of histologic diagnosis of all patients (n =23,786).

Histologic diagnosis	No. (%)
UPS^a/MFH^b	6,979 (29.3)
Leiomyosarcoma	3,581 (15.1)
Liposarcoma	3,437 (14.4)
Myxofibrosarcoma	1,837 (7.7)
Synovial sarcoma	1,256 (5.3)
Spindle cell sarcoma	1,110 (4.7)
Malignant peripheral nerve sheath tumour	966 (4.1)
Hemangiosarcoma (Angiosarcoma)	504 (2.1)
Fibrosarcoma	421 (1.8)
Rhabdomyosarcoma	393 (1.7)
Epithelioid sarcoma	265 (1.1)
Extraskeletal osteosarcoma	249 (1.0)
Others	2,788 (11.7)

[a] - UPS = undifferentiated pleomorphic sarcoma

[b] - MFH= malignant fibrous histiocytoma.

Table 2.

Univariate and Multivariate Cox Proportional Hazard Model for OS [a].

	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Total Number of patients				
Sex				
Male	Reference		Reference	
Female	0.92 (0.88–0.95)	< 0.001	0.92 (0.88–0.96)	< 0.001
Age				
64	Reference		Reference	
65	2.00 (1.94–2.06)	< 0.001	1.53 (1.43–1.65)	< 0.001
Race				
White	Reference		Reference	
Black	1.05 (0.98–1.12)	0.156	0.98 (0.91–1.07)	0.692
Asian	0.85 (0.74–0.97)	0.015	0.89 (0.77–1.04)	0.135
Others	0.97 (0.80–1.16)	0.712	0.88 (0.70–1.09)	0.245
Facility type				
Academic	Reference		Reference	
Comprehensive community	1.10 (1.05–1.15)	< 0.001	1.03 (0.97–1.08)	0.355
Community	1.11 (1.01–1.22)	0.039	1.03 (0.92–1.14)	0.644
Others	1.02 (0.95–1.08)	0.612	1.01 (0.94–1.08)	0.773
Insurance status				
Private insurance	Reference		Reference	
Medicaid	1.50 (1.37–1.64)	< 0.001	1.50 (1.34–1.68)	< 0.001
Medicare	2.06 (1.98–2.15)	< 0.001	1.37 (1.27–1.47)	< 0.001
Other government	1.76 (1.50–2.06)	< 0.001	1.57 (1.30–1.89)	< 0.001
Uninsured	1.39 (1.24–1.56)	< 0.001	1.45 (1.25–1.67)	< 0.001
Zip-code level income, $				
<38,000	Reference			
38,000–47,999	0.90 (0.84–0.96)	0.001	0.91 (0.84–0.98)	0.017
48,000–62,999	0.88 (0.82–0.93)	< 0.001	0.91 (0.84–0.99)	0.023

	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
>63,000	0.76 (0.72–0.81)	< 0.001	0.89 (0.81–0.97)	0.006
Zip-code education level				
21%	Reference		Reference	
13–20.9%	0.99 (0.93–1.05)	0.751	1.01 (0.93–1.08)	0.897
7–12.9%	0.90 (0.85–0.96)	0.001	0.94 (0.87–1.02)	0.135
<7%	0.81 (0.76–0.86)	< 0.001	0.87 (0.80–0.95)	0.002
Charlson Deyo score				
0	Reference		Reference	
1	1.47 (1.39–1.54)	< 0.001	1.22 (1.16–1.29)	< 0.001
2	2.05 (1.89–2.22)	< 0.001	1.59 (1.46–1.73)	< 0.001
Tumour location				
Upper extremity	Reference		Reference	
Lower extremity	1.03 (0.97–1.09)	0.340	0.99 (0.93–1.06)	0.763
Trunk	1.42 (1.34–1.51)	< 0.001	1.59 (1.46–1.73)	< 0.001
Histologic grade				
2	Reference		Reference	
3	1.92 (1.78–2.07)	< 0.001	1.41 (1.30–1.54)	< 0.001
4	1.89 (1.75–2.04)	< 0.001	1.38 (1.26–1.51)	< 0.001
AJCC[b] stage				
2	Reference		Reference	
3	1.87 (1.80–1.95)	< 0.001	1.70 (1.62–1.79)	< 0.001
Surgical margin				
Negative	Reference		Reference	
Positive	1.63 (1.55–1.71)	< 0.001	1.44 (1.37–1.52)	< 0.001
TTI[c]				
0–30	Reference		Reference	
31–60	1.10 (1.05–1.16)	< 0.001	1.08 (1.02–1.14)	0.011
61–90	1.18 (1.08–1.29)	< 0.001	1.11 (1.00–1.22)	0.044
91–	1.21 (1.07–1.36)	0.002	1.22 (1.07–1.39)	0.003

[a] - OS = overall survival

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b-AAJCC = American Joint Committee on Cancer

c- TTI = time to treatment initiation.

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Table 3.

Multivariate analysis for incidence rate ratio on TTI[a].

	Multivariate analysis	
	IRR[b] on TTI (95% CI)	*P* value
Total No. of patients		
Sex		
Male	Reference	
Female	1.04 (1.03–1.05)	< 0.001
Age		
64	Reference	
65	1.00 (0.99–1.01)	0.554
Race		
White	Reference	
Black	1.09 (1.08–1.10)	< 0.001
Asian	1.03 (1.01–1.05)	0.001
Others	1.12 (1.09–1.15)	< 0.001
Facility type		
Academic	Reference	
Comprehensive community	0.76 (0.75–0.77)	< 0.001
Community	0.64 (0.63–0.65)	< 0.001
Others	0.86 (0.85–0.87)	< 0.001
Insurance status		
Private insurance	Reference	
Medicaid	1.34 (1.33–1.36)	< 0.001
Medicare	1.12 (1.11–1.13)	< 0.001
Other government	1.18 (1.15–1.21)	< 0.001
Uninsured	1.17 (1.15–1.19)	< 0.001
Zip-code level income, $		
<38,000	Reference	
38,000–47,999	1.05 (1.04–1.06)	< 0.001
48,000–62,999	1.07 (1.06–1.08)	< 0.001
>63,000	1.06 (1.05–1.08)	< 0.001
Zip-code education level		
21%	Reference	
13–20.9%	0.95 (0.94–0.96)	< 0.001
7–12.9%	0.94 (0.93–0.95)	< 0.001
<7%	0.90 (0.88–0.91)	< 0.001
Charlson Deyo score		
0	Reference	
1	1.06 (1.05–1.06)	< 0.001
2-	1.15 (1.13–1.16)	< 0.001
Tumour location		

	Multivariate analysis	
	IRR[b] on TTI (95% CI)	P value
Upper extremity	Reference	
Lower extremity	1.15 (1.14–1.16)	< 0.001
Trunk	1.03 (1.02–1.04)	0.020
Histologic grade		
2	Reference	
3	0.85 (0.84–0.86)	< 0.001
4	0.88 (0.87–0.89)	< 0.001
AJCC[c] stage		
2	Reference	
3	1.29 (1.28–1.30)	< 0.001
Transition in care		
No	Reference	
Yes	1.62 (1.61–1.63)	< 0.001

[a] - TTI = time to treatment initiation;

[b] - IRR = incident rate ratio;

[c] - AJCC = American Joint Committee on Cancer.

[*] Incidence Rate Ratio means for every 1-point increase in the independent variable, the rate of TTI (in days) would change by a factor of that value, while holding all other variables in the model constant.