

Impact and Trends in Treatment Delay for High-Grade, Localized Undifferentiated Pleomorphic Sarcoma

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INTRODUCTION:

Time to treatment initiation (TTI) is linked to survival in several malignancies. However, its role in soft tissue sarcomas – particularly high-grade, undifferentiated pleomorphic sarcoma (UPS) – remains unclear. Evaluation of individual histologic subtypes enables a more patient-centered treatment approach.

METHODS:

Patients diagnosed with localized, high-grade UPS between 2004 and 2021 were identified retrospectively from the National Cancer Database. Following exclusion of cases with metastatic disease, low-grade tumors, missing outcome data, palliative treatment, or TTI ≥ 365 days, 6,220 patients were included. TTI was assessed both categorically (<4 vs ≥4 weeks) and continuously. Kaplan-Meier and multivariable Cox proportional hazards models adjusted for demographic, clinical, and socioeconomic factors were used to evaluate the association between TTI and overall survival (OS). Subgroup analysis by tumor location was performed.

RESULTS: Among 6,220 eligible patients, TTI significantly increased over time, rising from a median of 2.29 weeks in 2004 to 4.71 weeks in 2021. Patients with Medicaid experienced the longest delays (median 4.00 weeks), while uninsured patients had the shortest TTI (3.00 weeks), despite representing a minority of the cohort. Notably, referral rates to specialized centers remained stable over time. On multivariable analysis, prolonged TTI was independently associated with worse OS (HR = 1.01 per week; P = 0.032). In subgroup analysis, the negative effect of delay was observed in the extremity and trunk tumors (HR = 1.02; P = 0.006) but not in the head and neck (HR = 0.99; P = 0.820) or abdomen and pelvis (HR = 1.01; P = 0.768). TTI beyond four weeks was associated with significantly lower five-year OS (P < 0.001).

DISCUSSION AND CONCLUSION: Prolonged TTI is independently associated with decreased survival in patients with localized, high-grade UPS. These results reinforce prior evidence in soft tissue sarcomas, and emphasize the importance of treatment initiation within four weeks of diagnosis to improve outcomes in this aggressive sarcoma subtype. Rising TTI over the last two decades also presents a growing threat to survival in high-grade UPS. The commonly proposed explanation of transition of care to specialized centers does not fully account for this trend, as referral rates remained stable over the years. Increased use of FDG-PET and new molecular diagnostic tools may contribute to diagnostic delays. Systemic barriers, including insurance-driven prior authorization, potentially play a critical role. Policy reforms such as expedited approvals for high-grade sarcoma treatments may help reduce TTI.

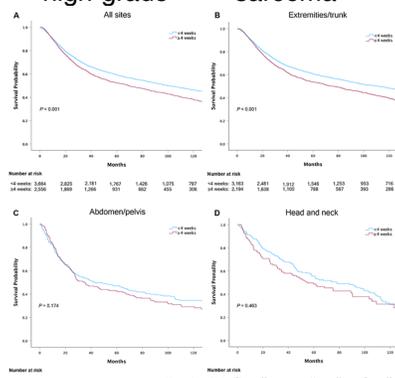
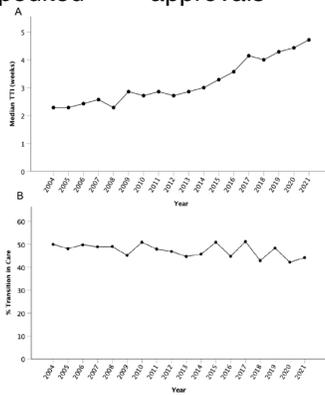


Table 3. Univariable and multivariable relationship between TTI and overall survival

Parameter	HR	95% CI	P-Value	HR	95% CI	P-Value
Time to treat, weeks	1.01	1.02-1.01	<0.001	1.01	1.00-1.02	<0.001
Age, years	0.97	0.96-0.98	<0.001	0.97	0.96-0.98	<0.001
15-59 vs ≥60	0.12	0.28-0.57	<0.001	0.64	0.37-0.84	<0.001
60-69 vs ≥70	0.27	0.44-0.57	<0.001	0.56	0.35-0.82	<0.001
70-79 vs ≥80	0.45	0.79-0.91	<0.001	0.84	0.79-0.91	<0.001
Sex						
Female vs. male	1.00			1.00		
Race						
Black vs. White	1.03	0.99-1.08	0.013	1.03	0.99-1.08	0.009
Other vs. White	0.73	0.60-0.89	<0.001	0.80	0.69-0.92	<0.001
Charlson-Deyo Score						
1 vs. 0	1.46	1.39-1.53	<0.001	1.17	1.09-1.26	<0.001
2 vs. 0	1.78	1.53-2.08	<0.001	1.46	1.29-1.74	<0.001
3+ vs. 0	2.49	2.07-3.00	<0.001	1.94	1.57-2.40	<0.001
Facility type						
Comprehensive cancer program vs. academic/non-academic program	1.04	0.96-1.14	0.313	0.91	0.83-1.00	0.051
Comprehensive cancer program vs. academic/cancer program	1.28	1.05-1.56	<0.001	1.05	0.95-1.16	0.247
Integrated cancer program vs. academic/non-academic program	1.13	1.02-1.24	0.014	1.04	0.95-1.14	0.290
Insurance coverage						
Uninsured vs. private insurance/managed care	1.66	1.32-2.07	<0.001	1.66	1.29-2.14	<0.001
Uninsured vs. private insurance/managed care	1.25	1.01-1.55	<0.001	1.46	1.23-1.74	<0.001
Medicaid vs. private insurance/managed care	2.19	1.82-2.57	<0.001	1.34	1.20-1.50	<0.001
Other vs. private insurance/managed care	1.67	1.39-1.97	<0.001	1.14	0.98-1.34	0.175
Income quartile						
1st Quartile vs. 1st Quartile (lowest)	0.95	0.85-1.07	0.360	0.97	0.85-1.11	0.617
2nd Quartile vs. 1st Quartile (lowest)	0.84	0.73-0.95	<0.001	0.91	0.80-1.04	0.170
3rd Quartile vs. 1st Quartile (lowest)	0.73	0.62-0.85	<0.001	0.83	0.73-0.94	<0.001
Distance to facility, miles						
25-50 vs. <25	1.04	0.94-1.16	0.448	-	-	-
50-75 vs. <25	1.14	0.99-1.31	0.073	-	-	-
75-99 vs. <25	1.46	0.96-2.20	0.070	-	-	-
≥100 vs. <25	0.95	0.58-1.51	0.824	-	-	-
Year of diagnosis	0.99	0.99-1.00	0.100	-	-	-
Primary site						
Head/neck vs. Extremity/trunk	1.34	1.19-1.50	<0.001	1.29	1.07-1.55	<0.001
Abdomen/pelvis vs. Extremity/trunk	1.15	1.01-1.31	<0.001	1.01	1.00-1.02	<0.001
Stage						
≥5.0 cm vs. <5.0 cm	1.82	1.67-1.99	<0.001	1.74	1.54-1.97	<0.001
Clinical Stage						
Stage 1 vs. Stage 2	1.50	1.40-1.62	<0.001	1.163	1.05-1.28	0.005
Treatment received						
Chemotherapy vs. Surgery	0.73	0.64-0.82	<0.001	0.74	0.64-0.84	<0.001
Radiation vs. Surgery	1.17	1.01-1.35	<0.001	1.00	0.92-0.99	0.029
Other vs. Surgery	1.17	0.92-1.45	0.101	0.97	0.73-1.27	0.827
Surgical Margins						
Positive vs. Negative	1.24	1.46-1.10	<0.001	1.24	1.21-1.28	<0.001
Positive vs. Negative	1.18	1.07-1.30	<0.001	1.23	1.07-1.52	<0.001
Number of sites						
1 vs. 2	1.20	1.12-1.28	<0.001	1.13	1.05-1.22	0.002
Number of sites						
1 vs. 2	0.92	0.83-1.04	0.180	0.94	0.83-1.07	0.351
1 vs. 3	0.84	0.63-1.05	0.201	0.90	0.66-1.11	0.718
1 vs. 4	0.78	0.33-0.87	<0.001	0.86	0.31-1.01	0.061

*Values correspond to univariable and multivariable Cox regression models. Hazard ratios (HR) and 95% confidence intervals (CI) are presented. Statistical significance relationships (P < 0.05) are bolded. TTI = time to treatment initiation.