Association of Postoperative Infection with Soft Tissue Sarcoma Resection Outcomes

Neslihan Erbasi[1], Molly Joyce, Sarah E. Lindsay[2], Yee-Cheen Doung, Kenneth Robert Gundle[2], James B Hayden, Duncan Ramsey[1]
[1]Oregon Health and Science University, [2]Oregon Health & Science University

INTRODUCTION:

Soft tissue sarcomas (STS) are a heterogenous group of rare malignancies of mesenchymal origin with more than 100 histologic subtypes. Advances in imaging, radiation, and surgical technique have resulted in major changes in the management of STS in recent years. Approximately 90% of previously unresectable extremity STS (ESTS) cases have been converted to limb-preservation surgeries.

However, STS resections can be complicated by major wound complications (MWC). Risk factors associated with MWC include patient characteristics (age, BMI, smoking history, diabetes), tumor characteristics (size, location, skin proximity), treatment variables (radiation therapy (XRT), chemotherapy), and surgical closure types (primary, staged, skin grafts, free vs rotational flap). Postoperative infection (POI) is a subset of MWC that happens in 5-12% of primary STS patients. POI following osteosarcoma resection has been shown to be associated with potential survival benefits, with infections possibly serving as immune checkpoint inhibitors. The association of POI with STS resection outcomes has not been well studied. A single 2014 study by Behnke *et al* evaluated STS patients with and without POI and found no difference in survival, local recurrence, or metastasis.

Our goal was to expand this line of inquiry with a larger cohort and a different patient population to determine whether POIs were correlated with distant metastasis (DM), 5-year overall survival (OS), or 5-year disease-specific survival (DSS).

METHODS:

A retrospective case review was conducted of patients with ESTS that underwent surgical resection at a single tertiary sarcoma and referral center from 2008-2023. Patients were divided into two groups: those who developed POI following STS resection and those who did not. Patient characteristics were compared between the two groups using Pearson's Chi-squared test and Welch Two Sample t-tests.

A total of 691 participants were identified. To determine DSS and OS, we utilized Surveillance, Epidemiology, and End Results (SEER) Cause-Specific Death Classification. Seven participants were excluded due to missing or unknown cause of death for further analysis. Primary outcomes were compared using Pearson's Chi-squared test. Survival curves for metastasis-free survival, OS, and DSS were analyzed using Cox Proportional Hazard (CPH) models and presented using Kaplan-Meier methods (n= 684 participants; n=172 with POI). Multivariable adjusted CPH models were used to calculate hazard ratios (HR). Statistical software R was used for analyses. P-values of less than 0.05 were considered statistically significant.

RESULTS:

Patient groups were equally matched, in terms of sex ($p=0.11$) and age at the time of surgery ($p=0.75$). Median BMI was significantly larger in the POI group compared to without ($p<0.001$). Smoking status ($p=0.077$) and diagnosis of diabetes ($p=0.056$) were not statistically significant between the groups. The presence of STS in the lower extremity ($p<0.001$) and tumor grade ($p=0.015$) were significantly higher and tumor size was significantly larger ($p<0.001$) in the POI group. Microscopic margins were not statistically different ($p=0.26$). The number of patients who received XRT ($p<0.001$), chemotherapy ($p=0.001$), or who presented with a metastatic disease($p=0.008$) was significantly higher in the POI group.

OS was significantly lower in the POI group ($p=0.019$), however presence of POI did not have a statistically significant effect on the DM ($p=0.37$) or DSS ($p=0.082$) (Table 2). The risk of DM, OS, and DSS among those who developed POI was 0.97 (95% CI: 0.45, 2.12), 1.60 (95%CI: 0.73, 3.53), and 1.01 (95% CI: 0.73, 1.41) respectively. There was no difference in DM ($p=0.95$), OS ($p=0.25$), and DSS ($p=0.95$) between patients with or without POI (Figure 1).

A competing risk model demonstrated positive margins, increased tumor size, higher tumor grade, and metastasis at presentation increased the risk of all oncologic outcomes. In contrast, receiving XRT was associated with improved DM, OS, and DSS (Table 3).

DISCUSSION AND CONCLUSION:

In our study, tumor grade was the greatest predictor of all oncologic outcomes followed by metastasis at presentation. Previous data showed getting XRT is a risk factor for MWC including POI. However, our study showed protective effect of the XRT in completing risk analysis. This apparent protective effect is likely not causative but rather due to lack of patients who qualified for XRT due to advanced disease course.

In conclusion, there are no significant differences in long term oncologic outcomes between the ESTS resection patients who developed POI and those who did not. Nonetheless, developing POI delays adjuvant care, increases comorbidities, impacts quality of life, and causes burden to health care system.

Figure 1: Kaplan Meier Curves Survival Outcomes by Infection Status

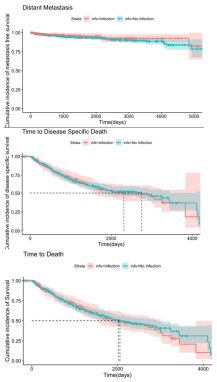

Table 1: Patient and Tumor Characteristics, by Postoperative Infection

Characteristic	Overall, N = 691[1]	No Infection, N = 516[1]	Infection, N = 175[1]	p-value[2]
Sex				0.11
Female	316 (46%)	245 (47%)	71 (41%)	
Male	375 (54%)	271 (53%)	104 (59%)	
Age at Date of Surgery (yrs)	63 (48, 72)	63 (48, 72)	62 (48, 72)	0.75
BMI (kg/m^2)	27 (24, 32)	27 (24, 31)	29 (26, 35)	<0.001
Smoker	74 (11%)	49 (9.5%)	25 (14%)	0.077
Diabetes	93 (13%)	62 (12%)	31 (18%)	0.056
Tumor Site: Lower vs Upper Extremity				<0.001
Upper Extremity	240 (35%)	212 (41%)	28 (16%)	
Lower Extremity	451 (65%)	304 (59%)	147 (84%)	
Tumor Size (cm)	8 (4, 13)	7 (4, 12)	10 (5, 16)	<0.001
Tumor Depth				0.093
Superficial	154 (22%)	123 (24%)	31 (18%)	
Deep	537 (78%)	393 (76%)	144 (82%)	
Tumor Grade				0.015
G1	97 (14%)	83 (16%)	14 (8.0%)	
G2	152 (22%)	116 (22%)	36 (21%)	
G3	442 (64%)	317 (61%)	125 (71%)	
Microscopic Margin				0.26
Negative	523 (76%)	385 (75%)	138 (79%)	
Positive	168 (24%)	131 (25%)	37 (21%)	
Radiotherapy (Y/N)	379 (55%)	258 (50%)	121 (69%)	<0.001
Radiotherapy				<0.001
No	216 (31%)	176 (34%)	40 (23%)	
Neoadjuvant only	269 (39%)	172 (33%)	97 (55%)	
Adjuvant only	89 (13%)	71 (14%)	18 (10%)	
Both	21 (3.0%)	15 (2.9%)	6 (3.4%)	
> 3 months ago	96 (14%)	82 (16%)	14 (8.0%)	
Chemotherapy (Y/N)	196 (28%)	130 (25%)	66 (38%)	0.001
Metastasis at Presentation	100 (14%)	64 (12%)	36 (21%)	0.008

[1] n (%); Median (IQR)
[2] Pearson's Chi-squared test; Welch Two Sample t-test

Table 2: Outcome Data by Presence of Post Operative Infection

Characteristic	Overall, N = 684[1]	No Infection, N = 512[1]	Infection, N = 172[1]	p-value[2]
Disease-specific Death				0.082
Alive or Dead of Other Cause	485 (71%)	372 (73%)	113 (66%)	
Dead of Disease	199 (29%)	140 (27%)	59 (34%)	
Distant Metastasis				0.37
None	638 (93%)	475 (93%)	163 (95%)	
Disease Metastasized	46 (6.7%)	37 (7.2%)	9 (5.2%)	
Survival				0.019
Alive	463 (68%)	359 (70%)	104 (60%)	
Dead	221 (32%)	153 (30%)	68 (40%)	

[1] n (%)
[2] Pearson's Chi-squared test

Table 3: Competing Risk Analysis for Factors Affecting Oncological Outcomes

	Disease Specific Death			Distant Metastasis			Overall Survival		
Characteristic	HR[1]	95% CI[1]	p-value	HR[1]	95% CI[1]	p-value	HR[1]	95% CI[1]	p-value
Infection									
No Infection	—	—		—	—		—	—	
Infection	0.99	0.71, 1.38	>0.9	0.97	0.44, 2.14	>0.9	1.07	0.78, 1.45	0.7
Age at Date of Surgery (yrs)	1.00	0.99, 1.01	0.5	1.00	0.98, 1.01	0.6	1.00	0.99, 1.01	0.5
Tumor Site: Lower vs Upper Extremity									
Upper Extremity	—	—		—	—		—	—	
Lower Extremity	0.77	0.55, 1.07	0.12	0.72	0.39, 1.33	0.3	0.76	0.56, 1.04	0.088
Tumor Depth									
Superficial	—	—		—	—		—	—	
Deep	1.51	0.96, 2.38	0.074	1.34	0.62, 2.88	0.5	1.32	0.88, 1.99	0.2
Radiotherapy (Y/N)	0.68	0.50, 0.92	0.011	0.40	0.21, 0.78	0.007	0.73	0.55, 0.97	0.029
Microscopic Margin									
Negative	—	—		—	—		—	—	
Positive	2.02	1.49, 2.73	<0.001	2.14	1.13, 4.06	0.020	1.76	1.31, 2.36	<0.001
Tumor Size (cm)	1.03	1.01, 1.05	0.010	0.93	0.88, 1.0	0.033	1.03	1.00, 1.05	0.023
Tumor Grade	2.60	1.49, 4.52	<0.001	12.4	1.67, 92.2	0.014	2.37	1.43, 3.93	<0.001
Metastasis at Presentation	2.26	1.61, 3.17	<0.001	3.82	1.93, 7.57	<0.001	2.21	1.59, 3.06	<0.001

[1] HR = Hazard Ratio, CI = Confidence Interval