Multi-Agent Chemotherapy for Surgically-Treated Soft Tissue Sarcomas Arising from Bone is Not Associated with Improved Survival Versus Surgery Alone: A Propensity-Matched, National Cancer Database Study.

Sean V. Cahill, MD[1]; Kristin E. Yu, BA[2]; Courtney S. Toombs, MD[2]; Dieter M. Lindskog, MD[2]

[1]Washington University in St. Louis, Department of Orthopaedic Surgery, St. Louis, MO, USA

[2]Yale University School of Medicine, Department of Orthopaedics and Rehabilitation, New Haven, CT, USA

Background

- Soft tissue sarcomas arising from bone are rare cancers with unestablished treatment protocols.
- Surgery is standard of care for soft tissue sarcomas.
- Multi-agent chemotherapy (MAC) decreases soft tissue sarcoma progression compared to single-agent chemotherapy.
- **Primary objective**: Is the addition of MAC with surgical resection associated with improved survival in treatment of soft tissue sarcomas arising from bone?
- **Secondary objectives**: What factors influence the decision to treat with MAC? Is response histology-specific?

Materials and Methods

Data

- National Cancer Database (NCDB), years 2004-2014
- Included: Adults with primary malignant sarcomas of bone who underwent surgical tumor resection
- Excluded: Primary bone tumors (e.g. osteosarcoma), single-agent chemo, incomplete survival data
- Control group = surgery only; Treatment = surgery + MAC

Statistics

- Propensity scores used to identify probability of receiving MAC for each subject, ranging from 0-1.
- An optimal, 1:1 match algorithm (using R) was used to match treatment and controls based on propensity scores
- Survival analyzed by Kaplan-Meier curves and the log-rank test. Survival was defined as time to death or censor.
- Subgroup analysis compared histology-specific survival
- Bonferroni correction was used, with resulting significance level set at p<0.001.

Table 1. 10 most common histologic diagnoses of soft-tissue sarcomas arising from bone, identified in the NCDB using ICD-O3 codes.

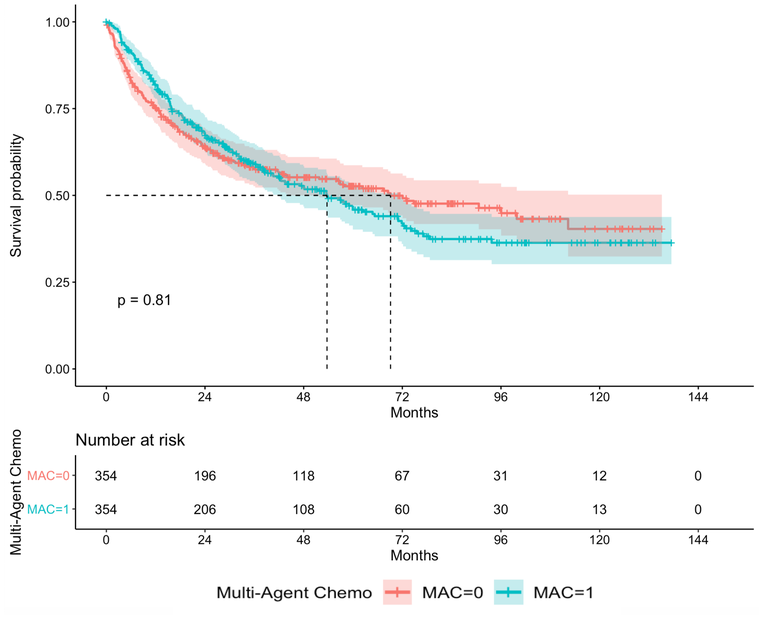
Histologic subtypes	Total:	902	% Total
Fibrous histiocytoma, malignant		178	20
Sarcoma, NOS		135	15
Giant cell sarcoma		107	12
Spindle cell sarcoma		99	11
Leiomyosarcoma subtypes		97	11
Hemangiosarcoma		84	9
Fibrosarcoma NOS		61	7
Undifferentiated sarcoma		43	5
Synovial sarcoma subtypes		34	4
Liposarcoma subtypes		27	3

Results

Table 2. Comparison of demographic and disease characteristics of patients with soft tissue sarcoma of bone between those receiving surgery alone versus those receiving surgery plus multi-agent chemotherapy (MAC). Results of propensity matching between treatment and controls are shown, demonstrating decreased differences between groups. Chi-squared and Mann-Whitney tests were used for analysis with significance level set at p<0.001.

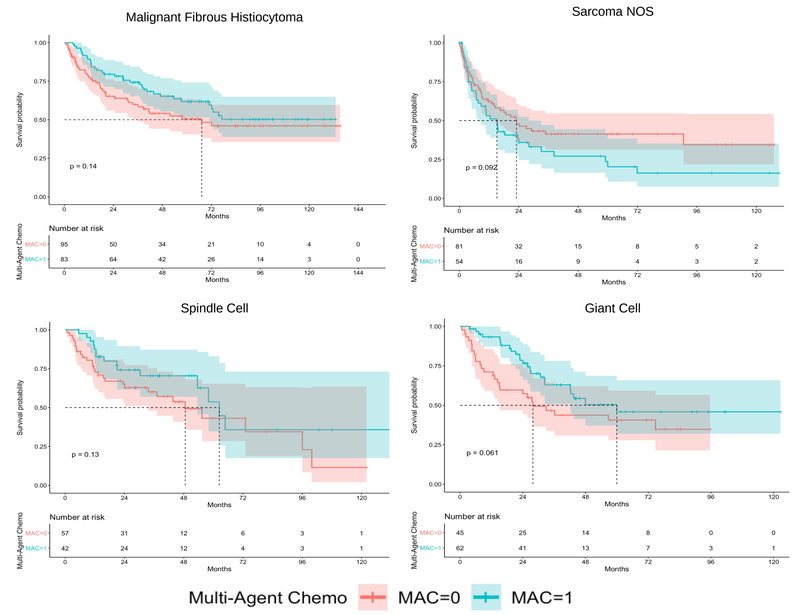
	Treatment		Control (before propensity match)			Control (after propensity match)		
	Surgery + MAC		Surgery only		p value	Surgery only		p value
Total	354	%	548	%		354	%	
Median age, years [IQR]	50 [21.25]		62 [25.75]		**<0.0001**	57 [22]		**<0.0001**
Sex								
Male	198	55.93	317	57.85	0.5705	198	55.93	>0.999
Female	156	44.07	231	42.15		156	44.07	
Race								
African American	44	12.43	56	10.22	0.433	38	10.73	0.8331
Asian	12	3.39	12	2.19		10	2.82	
Caucasian	293	82.77	469	85.58		302	85.31	
Other/Unknown	5	1.41	11	2.01		4	1.13	
Institution								
Academic	209	59.04	363	66.24	**<0.0001**	237	66.95	0.0029
Community	52	14.69	118	21.53		61	17.23	
Unknown	93	26.27	67	12.23		56	15.82	
Site								
Axial	284	80.23	142	25.91	**<0.0001**	85	24.01	**<0.0001**
Appendicular	66	18.64	394	71.90		264	74.58	
Not specified/unknown	4	1.13	12	2.19		5	1.41	
Size								
<10cm	202	57.06	323	58.94	**0.0006**	210	59.32	0.1312
≥10cm	103	29.10	108	19.71		82	23.16	
Unknown	49	13.84	117	21.35		62	17.51	
Grade								
Low	26	7.34	122	22.26	**<0.0001**	54	15.25	0.0010
High	275	77.68	311	56.75		236	66.67	
Unknown	53	14.97	115	20.99		64	18.08	
Metastasis at diagnosis								
No metastases	288	81.36	464	84.67	0.0685	299	84.46	0.2651
Distant metastases	60	16.95	67	12.23		46	12.99	
Unknown	6	1.69	17	3.10		9	2.54	

Figure 1. Propensity-matched survival, multi-agent chemo vs surgery alone. Kaplan-Meier survival analysis of matched cohort of patients with soft tissue sarcoma of bone receiving surgery alone versus surgery with multi-agent chemotherapy. Data shown with 95%CI. + indicates censored points. Dotted lines indicate 50% survival. P-value by log-rank test. 0=no MAC, 1=MAC.



Results

Figure 2. Unmatched survival associated with multi-agent chemotherapy based on histologic type. Data shown for 4 most common histologic sarcoma types with 95%CI. + indicates censored points. Dotted lines indicate 50% survival. P-value given by log-rank test. 0=no MAC, 1=MAC.



Discussion

Key Findings

- Addition of MAC to surgery for soft tissue sarcomas arising from bone is not associated with a survival benefit.
- MAC may contribute to worse overall survival, although a statistically significant survival difference was not identified.
- Select tumor types may benefit from MAC, although more investigation and larger samples are needed.
- MAC is more likely given for younger patients with high-grade tumors and axial lesions, despite unclear survival benefit

Considerations

- First study to examine the association of MAC with survival among patients with soft tissue tumors arising from bone
- Propensity matching reduced, but did not eliminate, differences between the treatment and control groups
- NCDB does not include data on progression-free survival, disease-specific mortality, and other important outcomes

Conclusion

Addition of multi-agent chemotherapy to surgical treatment of soft tissue sarcomas arising from bone is not associated with a survival benefit in this retrospective, propensity score-matched analysis.