acta orthopaedica belgica, 2024, 90, 745-758

doi.org/10.52628/90.4.12611

Non-Operative Ttreatment of patients with Chondrosarcoma: An analysis of patients who refused cancer-directed surgery or patients contraindicated to surgery

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Chondrosarcomas are the second most common primary bone sarcoma. Due to chondrosarcomas relative resistance to chemotherapy and radiation, surgical treatment has become the mainstay treatment option. The purpose of our study was to understand the proportion of patients in this population who undergo non-operative treatment options secondary to various reasons and analyze the difference in survival as well as patient and cancer specific characteristics between the two groups. We retrospectively reviewed the Surveillance, Epidemiology, and End Results (SEER) database for patients diagnosed with primary chondrosarcoma from 1973 to 2015. We evaluated the patients for both descriptive characteristics as well as cancer specific characteristics. We then performed a propensity matched analysis and other analyses to compare difference in cancer characteristics as well as survival. There were 3048 patients with chondrosarcoma of the bone during our study period of which 188(6.2%) patients did not undergo operative treatment either due to refusal of cancer directed surgery or contraindicated to surgery. A one unit increase in age was significantly associated with increased odds of not undergoing surgery(Odds Ratio 1.04;95% CI, 1.03-1.05). No statistically significant difference(P = 0.9) in survival was noted between patients with long bone, grade 1 chondrosarcomas regardless of if they did or did not undergo operative treatment. This study provides data to inform the patient on their decisions for or against surgery and may assist the surgeons in counseling patients regarding the surgical treatment of chondrosarcomas. Patients not undergoing operative treatment for chondrosarcomas are at statistically significantly increased risk of mortality.

Keywords: Chondrosarcoma, Atypical Central Cartilaginous Tumor, Non-operative treatment, survival.

INTRODUCTION

Chondrosarcomas are the second most common primary bone sarcoma, occurring with increasing frequency in those over the age 40[1]. Due to chondrosarcoma's relative resistance to chemotherapy and radiation, surgical resection is the definitive therapeutic intervention[2]. Although there have been numerous advancements in treatment options, electing for operative treatment is a difficult decision, and some patients may be hesitant to undergo surgery. Additionally, aging patients may be burdened by multiple comorbidities, some of which may take precedence in their healthcare decisions. In patients who have a contraindication to surgery or refuse recommended surgery, progression of disease may be more easily studied. To date, progression of disease for patients with chondrosarcomas without surgical treatment has not been well studied or detailed in the literature.

Here we sought to describe the demographic and oncologic differences in patients who did or did not undergo operative treatment. We also set out to describe survival and oncologic outcomes in patients treated non-operatively for chondrosarcoma.

METHODS

We retrospectively reviewed the Surveillance, Epidemiology, and End Results (SEER) database for patients diagnosed with primary chondrosarcoma from 1973 to 2015. Patients were included who had a confirmed diagnosis of chondrosarcoma and did not have a secondary diagnosis of any other cancer. When stratifying patients in the non-operative group we looked at patients who either had a contraindication to surgery due to other conditions or refused cancer directed surgery. This patient population of patients is a group that clinicians would have deemed to undergo

surgery but ultimately did not either secondary to a contraindication or refusal to undergo surgery.

Descriptive statistics were generated to provide an overview of patient demographics and cancer characteristics, such as age, race, cancer grade, etc. For categorical variables, frequency and percentages were reported, whereas the mean, standard deviation, and median and IQR were reported for continuous variables. Propensity-score matching using a greedy one to one match method was conducted; the model included 14 factors (age at diagnosis, year of diagnosis, sex, race, insurance, marital status at diagnosis, laterality, cancer grade, chemotherapy, radiation, tumor size, primary site, ICD, and cancer stage). Prior to Propensity-Score matching, Chi-square, Fisher's Exact, Independent two-sample t-test, Wilcoxon test, where appropriate, were used to compare characteristics between patients who underwent surgery and patients who did not.

Post propensity-score matching, a paired t-test, Mcnemar's, Symmetry test, where appropriate, were used to assess balance between groups. In addition, a logistic regression was used to examine risk factors of patients not undergoing surgery. Kaplan-Meier curves were created to observe survival in patients who underwent surgery and patients who did not, pre-matching and post-matching. Comparison of the two survival curves were made using the log rank test. Univariate and Multivariate Cox Proportional Hazard analyses were conducted to evaluate the risk of mortality and survival in different cases (i.e. all patients, patients who underwent surgery, and matched patients).

Additionally, four separate matching analyses were performed: a matching analysis in which patients were matched on cancer stage alone, cancer stage and other patient demographics/characteristics, cancer grade alone and cancer grade with other patient demographics/characteristics, respectively. An analysis between patients with grade 1 long bone

Table I. — Patient Demographics.

		Before Propensity Score-Matching			After Propensity Score-Matching		
Characteristic	All (N=3048)	Underwent Surgery N=2860 (93.8%)	Did not undergo Surgery N=188 (6.2%)	P-value	Underwent Surgery N=137 (50.0%)	Did not undergo Surgery Surgery N=137 (50.0%)	P-value
Age at diagnosis in years							
Mean (SD)	50.2 (17.9)	49.6 (17.4)	60.3 (21.9)	<0.0001	57.1 (18.6)	57.0 (21.3)	0.95
Median (IQR)	50.0 (37.0, 63.0)	50.0 (37.0, 62.0)	64.5 (43.5, 79.0)		58.0 (46.0, 70.0)	60.0 (41.0,75.0)	
Sex, n (%)							
Female	1411 (46.3%)	1321 (46.2%)	90 (47.9%)	0.65	60 (43.8%)	67 (48.9%)	0.39
Male	1637 (53.7%)	1539 (53.8%)	98 (52.1%)		77 (56.2%)	70 (51.1%)	
Race, n (%)							
Hispanic	367 (12.0%)	351 (12.3%)	16 (8.5%)		13 (9.5%)	14 (10.2%)	0.74
Non-Hispanic White	2335 (76.6%)	2191 (76.6%)	144 (76.6%)	0.20	110 (80.3%)	104 (75.9%)	
Non-Hispanic Black	178 (5.8%)	165 (5.8%)	13 (6.9%)		6 (4.4%)	10 (7.3%)	
Other	168 (5.5%)	153 (5.4%)	15 (8.0%)		8 (5.8%)	9 (6.6%)	
Insurance, n (%)							
Yes	1091 (35.8%)	1061 (37.1%)	30 (16.0%)		28 (20.4%)	18 (13.1%)	0.74
No	41 (1.4%)	38 (1.3%)	3 (1.6%)	<0.001	2 (1.5%)	3 (2.2%)	
Unknown	1916 (62.9%)	1761 (61.6%)	155 (82.5%)		107 (78.1%)	116 (84.7%)	
Marital Status, n (%)							
Single (never married)	700 (23.0%)	659 (23.0%)	41 (21.8%)		23 (16.8%)	29 (21.2%)	0.57
Married	1750 (57.4%)	1665 (58.2%)	85 (45.2%)		82 (59.9%)	67 (48.9%)	
Separated	26 (0.9%)	26 (0.91%)	0 (0%)	<0.001	--	--	
Divorced	225 (7.4%)	217 (7.6%)	8 (4.3%)		8 (5.8%)	6 (4.4%)	
Unmarried/Domestic Partner	1 (0.03%)	1 (0.03%)	0 (0%)		--	--	
Widowed	196 (6.4%)	157 (5.5%)	39 (20.7%)		17 (12.4%)	23 (16.8%)	
Unknown	150 (4.9%)	135 (4.7%)	15 (8.0%)		7 (5.1%)	12 (8.8%)	

chondrosarcomas was also performed comparing survival times between those undergoing and not undergoing surgical treatment.

All analyses were performed in SAS Enterprise Guide v8.3 (SAS, Inc.; Cary, NC). A $p<0.05$ was considered statistically significant. Our study was approved by our institutional review board (IRB) and deemed exempt from full IRB review process.

RESULTS

Patient Demographics

There were 3048 patients diagnosed with chondrosarcoma of the bone: a higher percentage of patients were Male (1637; 53.7%), Non-Hispanic White (2335; 76.6%), and Married (1750; 57.4%). The mean age at diagnosis was 50.2 ± 17.9 years. Patients who underwent surgery were more likely to have insurance [37.1% (1061) vs 16.0% (30)] and be married [58.2% (1665) vs 45.2% (85)] compared to patients who did not undergo surgery. There was a significant difference in the population of age at diagnosis ($P<0.001$) between patients who underwent surgery and patients who did not; the median age at diagnosis for patients who did not undergo surgery was higher in comparison to patients who underwent surgery (64.5 years vs 50.0 years, respectively). Table I provides detailed statistics on patient demographics.

Cancer Characteristics

Pertaining to cancer characteristics, a higher percentage of patients were diagnosed between 2006 and 2015 (1287; 42.2%), had a well-differentiated tumor (1135; 37.2%), and did not receive radiation treatment (2762; 90.6%). The majority of patients had a localized cancer stage (1655; 54.3%), followed by regional (1024; 33.6%), distant (218; 7.2%), and unstaged (151; 5.0%). There was a significant association between all the characteristics and surgery outcome. One of the significant characteristics was SEER historic stage ($P<0.001$); patients who underwent surgery were more likely to have a localized chondrosarcoma stage compared to patients who did not undergo surgery. Table II provides detailed statistics on cancer characteristics.

Predictors for not Undergoing Surgery

Of the patients who were diagnosed with Chondrosarcoma, 188 did not undergo surgery. A one unit increase in age was significantly associated with increased odds of not undergoing surgery (Odds Ratio (OR) 1.04; 95% CI, 1.03-1.05). Patients with unstaged cancer were 16 times more likely to not undergo surgery (OR 16.23; 95%CI 10.43-25.26), whereas, interestingly, patients with a left laterality had decreased odds of not undergoing surgery (OR 0.65; 95%CI 0.43-0.97). Table III provides detailed statistics on predictors of not undergoing surgery.

Risk Factors of Survival and Mortality

Compared to the well-differentiated reference group, patients with any type of cancer grade had an increased risk of mortality, with undifferentiated cancer grade having the highest increased risk of mortality (HR 8.72; 95% CI 7.04-10.81). Patients with a distant cancer stage had an increased risk of mortality compared to patients with localized cancer stage (HR 8.58; 95% CI 7.13-10.31), whereas, patients who did not receive radiation treatment were more likely to survive compared to patients who received radiation (HR 0.34; 95% CI 0.29-0.40). In addition, patients who did not undergo surgery had an increased risk of mortality compared to patients who underwent surgery (HR 3.45; 95% CI 2.87-4.14). In the matched sample, both age and surgery were significant risk factors of mortality and survival. Older patients (HR 1.03; 95% CI 1.01-1.05) and patients who did not undergo surgery (HR 2.10; 95% CI 1.36-3.24) had an increased risk of mortality. Table 4 provides more detailed statistics on risk factors of mortality/survival.

Table V and Table VI displays the multivariate Cox Proportional Hazards ratio for all patients and the matched sample, respectively. Although the hazards ratio for surgery reduced in the multivariate model for all patients and patients in the matched sample, there was still a significantly increased risk of mortality for patients who did not undergo surgery.

The log-rank test as well as the matched sample showed that there was a significant difference in survival time between the two groups ($P<0.0001$, Figure 1 and $P=0.002$, Figure 2, respectively); patients who underwent surgery had higher survival. In each cancer stage, the survival curves were higher for patients who had surgery compared to patients who did not when matched on cancer stage and patient characteristics (Figure 3) as well as when matched only on cancer stage alone (Figure 4).

Figure 5 displays the survival curves for each matched cancer grade when grade is the only variable patients were matched on. In unknown, well-differentiated, moderately differentiated, and poorly differentiated cancer grades, the survival curves were higher for patients who had surgery compared to patients who did not. Figure 6 displays the survival curves for each

Table II. — Patient Cancer Characteristics.

Characteristic		Before Propensity Score-Matching			After Propensity Score-Matching		
	All N=3048	Underwent Surgery N=2860 (93.8%)	Did not undergo Surgery N=188 (6.2%)	P-value	Underwent Surgery N=137 (50.0%)	Did not undergo Surgery N=137 (50.0%)	P-value
Year of diagnosis, n (%)							
1973 to 1983	341 (11.2%)	283 (9.9%)	58 (30.9%)	<0.001	31 (22.6%)	35 (25.6%)	0.29
1984 to 1994	385 (12.6%)	356 (12.5%)	29 (15.4%)		18 (13.1%)	24 (17.5%)	
1995 to 2005	1035 (34.0%)	972 (34.0%)	63 (33.5%)		55 (40.2%)	54 (39.4%)	
2006 to 2015	1287 (42.2%)	1249 (43.7%)	38 (20.2%)		33 (24.1%)	24 (17.5%)	
Laterality, n (%)							
Left	1143 (37.5%)	1104 (38.6%)	39 (20.7%)	<0.001	43 (31.4%)	32 (23.4%)	0.47
Right	1278 (41.9%)	1212 (42.4%)	66 (35.1%)		47 (34.3%)	54 (39.4%)	
Other	627 (20.6%)	544 (19.0%)	83 (44.2%)		47 (34.3%)	51 (37.2%)	
Grade, n (%)							
I-Well differentiated	1135 (37.2%)	1088 (38.0%)	47 (25.0%)	<0.001	37 (27.0%)	37 (27.0%)	>0.99
II- Moderately differentiated	1072 (35.2%)	1035 (36.2%)	37 (19.7%)		30 (21.9%)	30 (21.9%)	
III-Poorly differentiated	278 (9.1%)	261 (9.1%)	17 (9.0%)		12 (8.8%)	12 (8.8%)	
IV-Undifferentiated/anaplastic	180 (5.9%)	173 (6.1%)	7 (3.7%)		4 (2.9%)	4 (2.9%)	
Unknown	383 (12.6%)	303 (10.6%)	80 (42.6%)		54 (39.4%)	54 (39.4%)	
Chemotherapy, n (%)							
Yes	227 (7.5%)	201 (7.0%)	26 (13.8%)	0.001	12 (8.8%)	12 (8.8%)	>0.99
No/unknown	2821 (92.6%)	2659 (93.0%)	162 (86.2%)		125 (91.2%)	125 (91.2%)	
Radiation, n (%)							
Yes	286 (9.4%)	240 (8.4%)	46 (24.5%)	<0.001	25 (18.3%)	21 (15.3%)	0.54
No	2762 (90.6%)	2620 (91.6%)	142 (75.5%)		112 (81.8%)	116 (84.7%)	
SEER Historic Stage, n (%)							
Localized	1655 (54.3%)	1606 (56.2%)	49 (26.1%)	<0.001	39 (28.5%)	39 (28.5%)	>0.99
Regional	1024 (33.6%)	976 (34.1%)	48 (25.5%)		39 (28.5%)	39 (28.5%)	
Distant	218 (7.2%)	177 (6.2%)	41 (21.8%)		23 (16.8%)	23 (16.8%)	
Unstaged	151 (5.0%)	101 (3.5%)	50 (26.6%)		36 (26.3%)	36 (26.3%)	
Tumor Size, n (%)							
<8 cm	744 (24.4%)	732 (25.6%)	12 (6.4%)	<0.001	9 (6.6%)	9 (6.6%)	>0.99
8-15 cm	390 (12.8%)	376 (13.2%)	14 (7.5%)		7 (5.1%)	7 (5.1%)	
>15 cm	154 (5.1%)	143 (5.0%)	11 (5.9%)		5 (3.7%)	5 (3.7%)	
Unknown	1760 (57.7%)	1609 (56.3%)	151 (80.3%)		116 (84.7%)	116 (84.7%)	
ICD, n (%)							
Dedifferentiated	180 (5.9%)	177 (6.2%)	3 (1.6%)	0.01	3 (2.2%)	3 (2.2%)	>0.99
Juxtacortical	43 (1.4%)	43 (1.5%)	0 (0%)		--	--	
NOS	2825 (92.7%)	2640 (92.3%)	185 (98.4%)		134 (97.8%)	134 (97.8%)	
Primary site, n (%)							
Long bones: upper limb, scapula, and associated joints	552 (18.1%)	532 (18.6%)	20 (10.6%)	<0.001	22 (16.1%)	18 (13.1%)	0.27
Short bones of upper limb and associated joints	79 (2.6%)	76 (2.7%)	3 (1.6%)		6 (4.4%)	3 (2.2%)	
Long bones of lower limb and associated joints	1005 (33.0%)	961 (33.6%)	44 (23.4%)		37 (27.0%)	41 (29.9%)	
Short bones of lower limb and associated joints	87 (2.9%)	84 (2.9%)	3 (1.6%)		2 (1.5%)	2 (1.5%)	
Overlap of bones, joints	2 (0.07%)	1 (0.03%)	1 (0.5%)		--	--	
Bone of limb, NOS	8 (0.26%)	7 (0.2%)	1 (0.5%)		0 (0%)	1 (0.7%)	
Vertebral column	140 (4.6%)	133 (4.7%)	7 (3.7%)		8 (5.8%)	7 (5.1%)	
Rib sternum, clavicle, and associated joints	570 (18.7%)	551 (19.3%)	19 (10.1%)		27 (19.7%)	15 (11.0%)	
Pelvic bones, sacrum, coccyx, and associated joints	564 (18.5%)	482 (16.9%)	82 (43.6%)		32 (23.4%)	42 (30.7%)	
Overlap bones, joints, and art. Cartilage	8 (0.26%)	8 (0.3%)	0 (0%)		--	--	
Bone, NOS	33 (1.1%)	25 (0.9%)	8 (4.3%)		2 (2.2%)	8 (5.8%)	

Table III. — Predictors for not Undergoing Surgery.

Characteristic	Odds Ratios (95% CI)	P-value
Age at diagnosis, years	1.04 (1.03, 1.05)	<0.0001
Sex		
Male	1.00	0.65
Female	1.07 (0.80, 1.44)	
Insurance		
Yes	1.00	<0.0001
No	2.79 (0.82, 9.55)	
Unknown	3.11 (2.09, 4.63)	
Race		
Non-Hispanic White	1.00	0.20
Non-Hispanic Black	1.20 (0.67, 2.16)	
Hispanic	0.69 (0.41,1.18)	
Other	1.49 (0.86, 2.60)	
Marital status		
Married	1.00	<0.0001
Single (never married)	1.22 (0.83, 1.79)	
Unmarried/Domestic Partner	--	
Separated	--	
Divorced	0.72 (0.35, 1.51)	
Widowed	4.87 (3.22, 7.35)	
Unknown	2.18 (1.22, 3.87)	
Grade		
I-Well differentiated	1.00	<0.0001
II- Moderately differentiated	0.83 (0.53, 1.28)	
III-Poorly differentiated	1.51 (0.85, 2.67)	
IV-Undifferentiated/anaplastic	0.94 (0.42, 2.11)	
Unknown	6.11 (4.17, 9.00)	
Stage		
Localized	1.00	<0.0001
Regional	1.61 (1.07, 2.42)	
Distant	7.59 (4.88, 11.82)	
Unstaged	16.23 (10.43, 25.26)	
Laterality		
Right	1.00	<0.0001
Left	0.65 (0.43, 0.97)	
Other	2.80 (2.00, 3.93)	
Chemotherapy		
No	1.00	0.001
Yes	2.12 (1.37, 3.29)	
Radiation		
Yes	3.54 (2.47, 5.06)	<0.0001
No	1.00	
Tumor size		
<8 cm	1.00	<0.0001
8 cm- 15 cm	2.27 (1.04, 4.96)	
>15 cm	4.69 (2.03, 10.84)	
Unknown	5.72 (3.16, 10.37)	
ICD		
Dedifferentiated Chondrosarcoma	1.00	0.05
Juxtacortical Chondrosarcoma	--	
NOS Chondrosarcoma	4.13 (1.31, 13.07)	

Table IV. — Univariate Cox Proportional Hazard analysis.

Characteristic	All Patients N=3048		Underwent Surgery N=2860		All Patients Post-Matching N=274	
	Hazards Ratio (95% CI)	P-value	Hazards Ratio (95% CI)	P-value	Hazards Ratio (95% CI)	P-value
Age at diagnosis	1.05 (1.05, 1.06)	<0.0001	1.05 (1.05, 1.06)	<0.0001	1.03 (1.01, 1.05)	0.003
Sex						
Male	1.00		1.00		1.00	0.14
Female	0.76 (0.67, 0.86)	<0.0001	0.75 (0.66, 0.86)	<0.0001	1.56 (0.86, 2.81)	
Race						
Non-Hispanic White	1.00		1.00		1.00	
Non-Hispanic Black	0.79 (0.60, 1.04)	0.10	0.76 (0.56, 1.02)	0.07	1.82 (0.44, 7.42)	0.41
Hispanic	0.75 (0.60, 0.93)	0.01	0.82 (0.65, 1.03)	0.08	0.63 (0.20, 1.94)	0.42
Other	0.92 (0.70, 1.20)	0.52	0.83 (0.61, 1.12)	0.23	1.37 (0.38, 4.97)	0.63
Insurance						
Yes	1.00		1.00		1.00	
No	0.87 (0.41, 1.84)	0.71	0.69 (0.29, 1.68)	0.42	--	
Unknown	1.23 (1.05, 1.45)	0.01	1.11 (0.94, 1.32)	0.22	1.00 (0.29, 3.45)	>0.99
Marital Status						
Married	1.00		1.00		1.00	
Divorced	1.17 (0.94, 1.46)	0.17	1.14 (0.90, 1.45)	0.26	1.16 (0.30, 4.54)	0.83
Separated	1.26 (0.67, 2.35)	0.47	1.35 (0.72, 2.53)	0.34	--	--
Single (never married)	0.70 (0.59, 0.82)	<0.0001	0.66 (0.55, 0.79)	<0.0001	0.67 (0.28, 1.57)	0.35
Widowed	3.64 (3.04, 4.36)	<0.0001	3.48 (2.84, 4.27)	<0.0001	1.72 (0.70, 4.23)	0.24
Unknown	0.85 (0.61, 1.18)	0.33	0.82 (0.57, 1.18)	0.28	0.54 (0.10, 2.98)	0.48
Unmarried or Domestic Partner	--	--	--	--	--	--
Grade						
I-Well differentiated	1.00		1.00		--	--
II-Moderately differentiated	1.65 (1.39, 1.95)	<0.0001	1.71 (1.43, 2.03)	<0.0001	--	
III-Poorly differentiated	4.13 (3.35, 5.09)	<0.0001	4.40 (3.53, 5.49)	<0.0001	--	
IV-Undifferentiated/anaplastic	8.72 (7.04, 10.81)	<0.0001	9.95 (7.97, 12.44)	<0.0001	--	
Unknown	3.05 (2.54, 3.67)	<0.0001	2.61 (2.12, 3.21)	<0.0001	--	
Stage						
Localized	1.00		1.00		--	--
Distant	8.58 (7.13, 10.31)	<0.0001	8.03 (6.55, 9.85)	<0.0001	--	
Regional	2.25 (1.96, 2.58)	<0.0001	2.32 (2.01, 2.67)	<0.0001	--	
Unstaged	2.04 (1.58, 2.64)	<0.0001	1.56 (1.11, 2.18)	0.01	--	
Laterality						
Right	1.00		1.00		1.00	
Left	0.95 (0.82, 1.09)	0.45	0.97 (0.84, 1.13)	0.72	0.76 (0.35, 1.63)	0.48
Other	1.45 (1.25, 1.68)	<0.0001	1.28 (1.09, 1.51)	0.003	0.95 (0.50, 1.83)	0.88
Chemotherapy						
Yes	1.00		1.00		--	--
No/unknown	0.24 (0.21, 0.29)	<0.0001	0.23 (0.19, 0.27)	<0.0001	--	--
Radiation						
Yes	1.00		1.00		1.00	
No	0.34 (0.29, 0.40)	<0.0001	0.37 (0.31, 0.45)	<0.0001	0.58 (0.30, 1.13)	0.11
Tumor Size						
<8 cm	1.00		1.00		--	--
8-15 cm	3.13 (2.36, 4.16)	<0.0001	3.20 (2.38, 4.30)	<0.0001	--	--
>15 cm	5.01 (3.62, 6.93)	<0.0001	5.34 (3.81, 7.49)	<0.0001	--	--
Unknown	2.47 (2.00, 3.11)	<0.0001	2.29 (1.79, 2.92)	<0.0001	--	--
ICD						
Dedifferentiated Chondrosarcoma	1.00		1.00		1.00	
Juxtacortical Chondrosarcoma	0.046 (0.02, 0.13)	<0.0001	0.04 (0.02, 0.12)	<0.0001	--	
NOS Chondrosarcoma	0.17 (0.14, 0.21)	<0.0001	0.14 (0.12, 0.17)	<0.0001	0.33 (0.04, 3.21)	0.34
Surgery						
Yes	1.00		--	--	1.00	
No	3.45 (2.87, 4.14)	<0.0001	--	--	2.10 (1.36, 3.24)	0.001

Table V. — Multivariate Cox-Proportional Hazard analysis for all patients.

Characteristic	All Patients N=3048	
	Hazards Ratio (95% CI)	P-value
Age at diagnosis	1.05 (1.04, 1.05)	<0.0001
Sex		
Male	1.00	
Female	0.68 (0.60, 0.77)	<0.0001
Race		
Non-Hispanic White	1.00	
Non-Hispanic Black	0.93 (0.70, 1.22)	0.59
Hispanic	1.02 (0.82, 1.28)	0.84
Other	0.78 (0.59, 1.03)	0.08
Insurance		
Yes	1.00	
No	1.27 (0.59, 2.73)	0.54
Unknown	1.06 (0.86, 1.32)	0.59
Marital Status		
Married	1.00	
Divorced	1.58 (1.26, 2.00)	<0.0001
Separated	1.40 (0.74, 2.64)	0.30
Single (never married)	1.30 (1.09, 1.56)	0.005
Widowed	1.37 (1.12, 1.69)	0.003
Unknown	1.11 (0.79, 1.57)	0.54
Unmarried or Domestic Partner	--	--
Grade		
I-Well differentiated	1.00	
II-Moderately differentiated	1.34 (1.13, 1.59)	<0.0001
III-Poorly differentiated	2.08 (1.66, 2.61)	<0.0001
IV-Undifferentiated/anaplastic	3.23 (2.48, 4.19)	<0.0001
Unknown	1.78 (1.47, 2.17)	<0.0001
Stage		
Localized	1.00	
Distant	3.17 (2.58, 3.90)	<0.0001
Regional	1.50 (1.30, 1.74)	<0.0001
Unstaged	1.01 (0.76, 1.34)	0.94
Laterality		
Right	1.00	
Left	0.97 (0.84, 1.12)	0.67
Other	1.17 (1.00, 1.37)	0.05
Chemotherapy		
Yes	1.00	
No/unknown	0.54 (0.44, 0.66)	<0.0001
Radiation		
Yes	1.00	
No	0.60 (0.51, 0.72)	<0.0001
Tumor Size		
<8 cm	1.00	
8-15 cm	1.51 (1.13, 2.02)	0.0059
>15 cm	2.05 (1.47, 2.87)	<0.0001
Unknown	2.09 (1.59, 2.74)	<0.0001
ICD		
Dedifferentiated Chondrosarcoma	1.00	
Juxtacortical Chondrosarcoma	0.17 (0.06, 0.46)	0.0005
NOS Chondrosarcoma	0.52 (0.41, 0.67)	<0.0001
Surgery		
Yes	1.00	
No	1.89 (1.53, 2.34)	<0.0001

Table VI. — Multivariate Cox-Proportional Analysis for all patients in matched sample.

Characteristic	All Patients Post-Matching N=274	
	Hazards Ratio (95% CI)	P-value
Age at diagnosis	1.04 (1.03, 1.05)	<0.0001
Surgery		
Yes	1.00	
No	1.56 (1.13, 2.15)	0.01

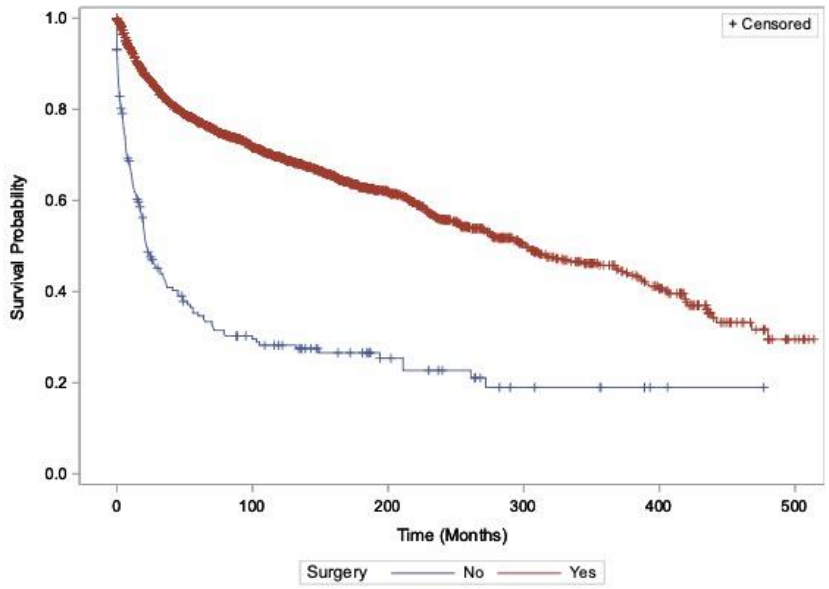

Fig. 1 — Comparison of Survival Kaplan-Meier Curves between patients who underwent surgery and patients who did not.

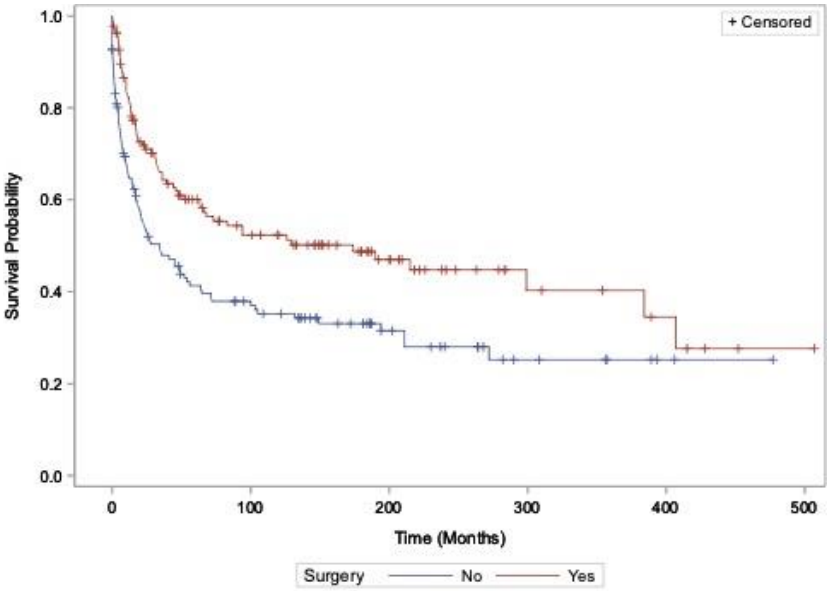

Fig. 2 — Comparison of Survival Kaplan-Meier Curves in matched sample between patients who underwent surgery and patients who did not.

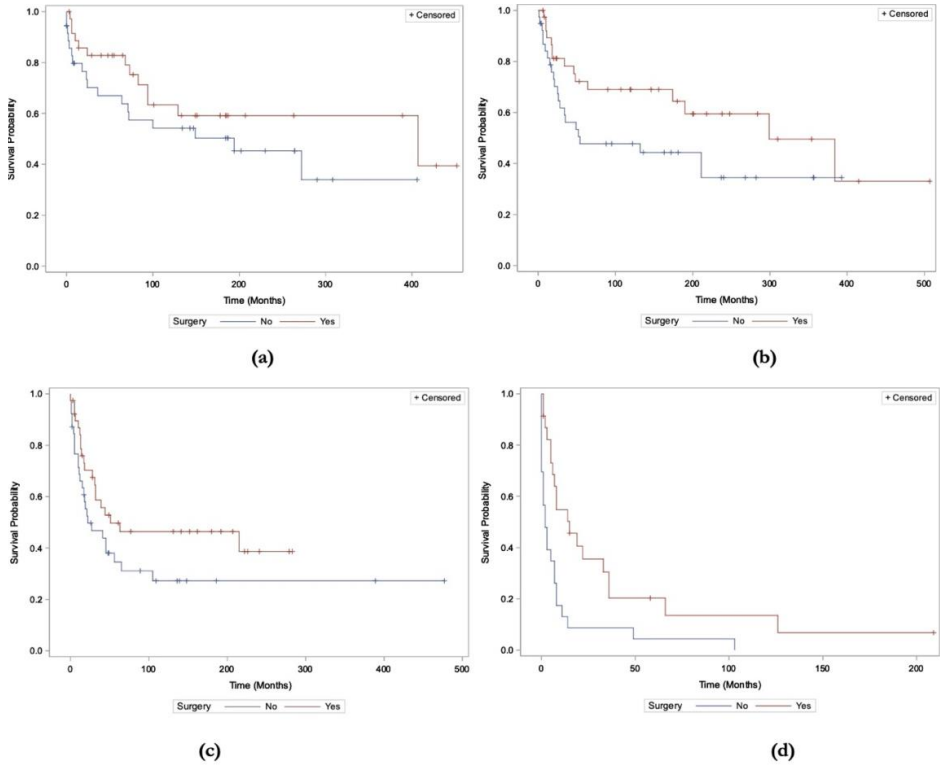

Fig. 3 — Survival Kaplan-Meier Curves in Matched Cancer Stages between patients who underwent surgery and patients who did not (Matching on Cancer Stage and other Patient Characteristics): a). Unstaged, (b) Localized Stage, (c) Regional Stage, (d) Distant Stage.

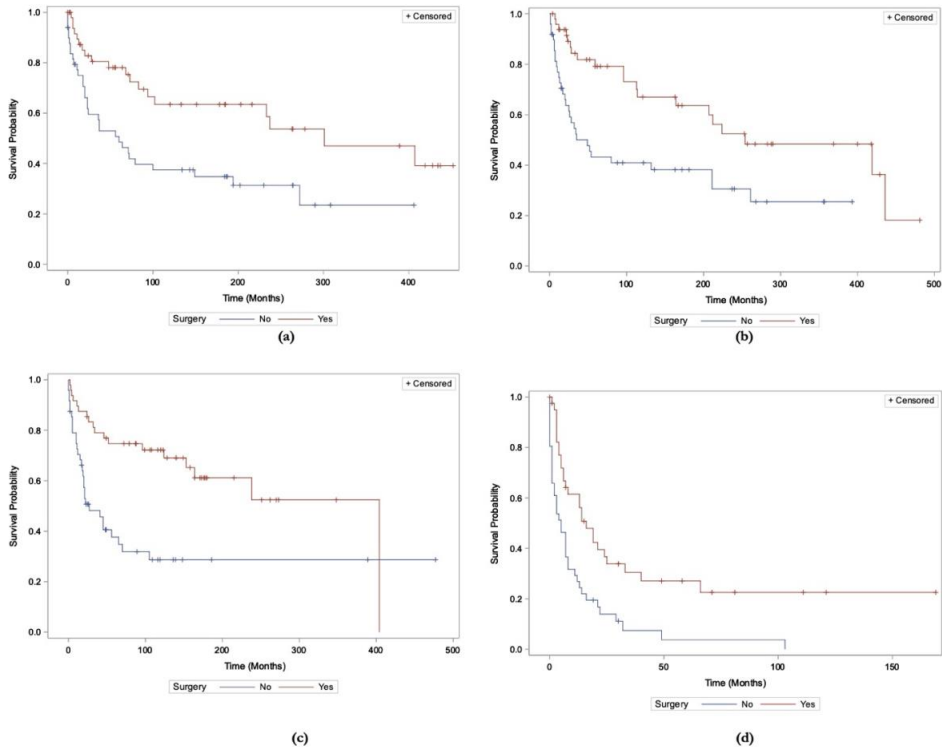

Fig. 4 — Survival Kaplan-Meier Curves in Matched Cancer Stages between patients who underwent surgery and patients who did not (Matching on Cancer Stage alone): (a). Unstaged, (b) Localized Stage, (c) Regional Stage, (d) Distant Stage.

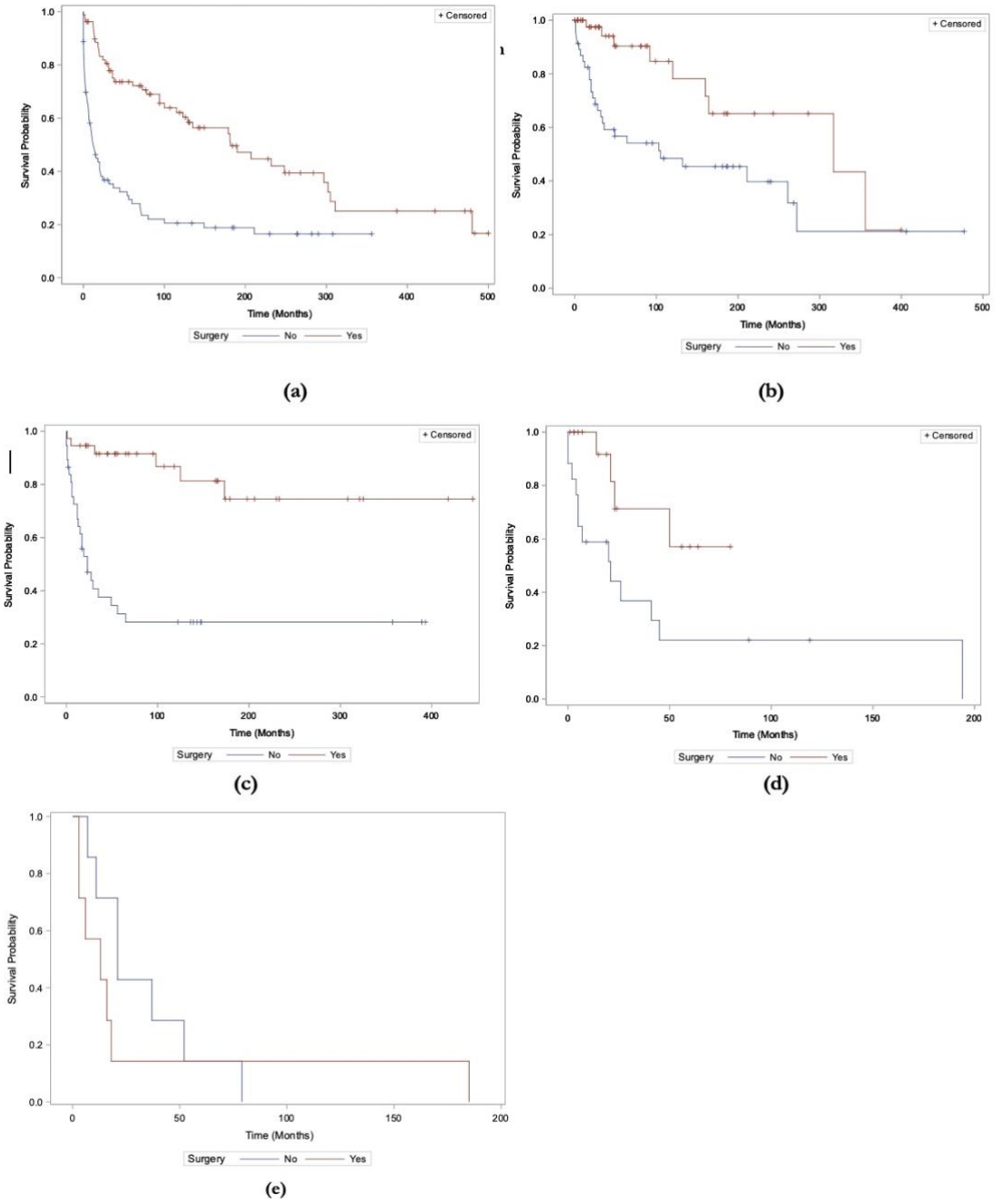

Fig. 5 — Survival Kaplan-Meier Curves in Matched Cancer Grade between patients who underwent surgery and patients who did not (Matching on Cancer Grade): (a) Unknown, (b) I-Well differentiated, (c) II-Moderately differentiated, (d) III-Poorly differentiated, (e) IV-Undifferentiated/anaplastic.

cancer grade in which patients were matched on cancer grade and other patient characteristics.

Long Bone Grade 1 Chondrosarcoma (or central atypical cartilaginous tumors)

No statistically significant difference (p=0.9) in survival was noted between patients with long bone, grade 1 chondrosarcomas regardless of if they did or did not undergo operative treatment (mean/average 137.6 vs 133.9 months, respectively). Log rank test was also conducted to compare median survival time between groups and was also found not to be statistically significant as well (p = 0.10; 404 vs 272 months, respectively).

DISCUSSION

Chondrosarcomas are one of the most common primary bone sarcomas. Traditional treatment includes primarily surgical resection with local adjuvants with little effect of chemotherapy and radiation[2]. Although

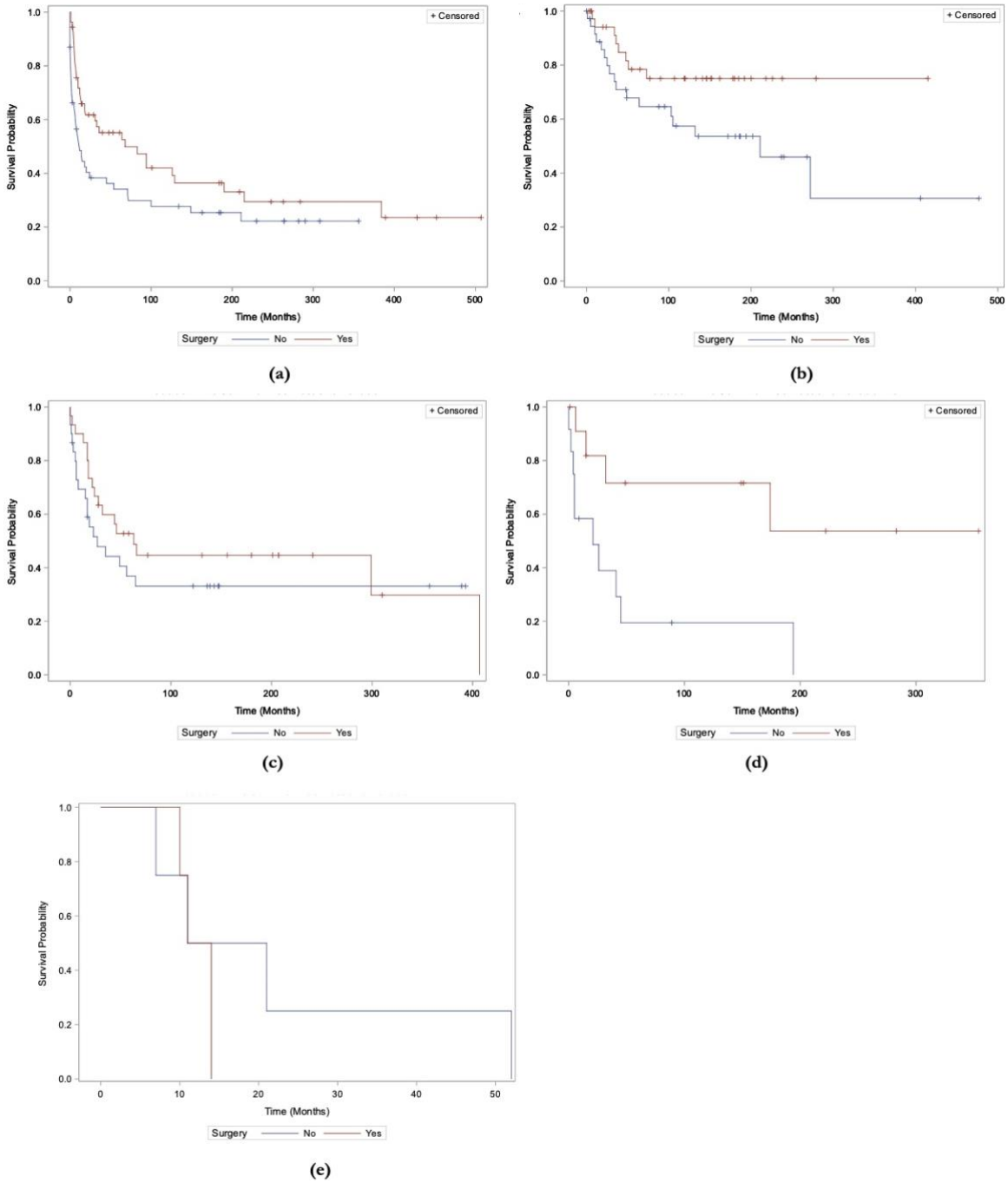

Fig. 6 — Survival Kaplan-Meier Curves in Matched Cancer Grade between patients who underwent surgery and patients who did not (Matching on Cancer Grade and other Patient Characteristics): (a) Unknown, (b) I-Well differentiated, (c) II-Moderately differentiated, (d) III-Poorly differentiated, (e) IV-Undifferentiated/anaplastic.

there is ongoing research in regarding advanced chondrosarcomas that may be initially resistant to cytotoxic chemotherapy, patients typically will elect to undergo surgical resection in a timely manner. Pelvic chondrosarcomas were additionally treated with hemipelvectomies which are associated with poor functional outcomes[3]. Given the extent of these large procedures and their potential complications, there are various patient specific factors that limit patients' ability to undergo surgical treatment. There is a lack of data that details the outcomes of non-operative treatment of these tumors. Our study aims to address the prognosis, outcomes and risk factors for patients who did not undergo surgical resection for their chondrosarcomas.

Risk Factors for Non-operative Treatment

A thorough analysis of risks for not undergoing surgery will better help providers target discussions

on operative and non-operative management with patients. In our study, increase in age was associated with an increased odds of not undergoing surgery. This may be a sequala of patients with increased age being at a higher risk of having multiple comorbidities and not being safe for undergoing surgical treatment. This is in accordance with previous studies that have found age to be associated with increased odds of refusing surgery in patients with non-small cell lung cancer, breast cancer, and hepatocellular carcinoma; however, mixed reports are found in patients with colon cancer[4-7].

Grade was not significantly associated with predicting decreased risk for non-operative treatment compared to stage where increased stage resulted in significantly higher risk for non-operative treatment. This aligns with the understood notion that stage is the most accurate predictor for mortality and patients with increased stage may elect to undergo other treatment options at a more advanced stage. Race and insurance status were not statistically significantly correlated with decreased risk of undergoing surgery. This is contrary to what has been seen in other malignancies such as colon and lung cancer[7,8]. In patients with non-small cell lung cancer, patients who identified as Black had almost 2 times higher odds of not undergoing surgical treatment[8].

Patients with advanced stage disease may also prefer to investigate other avenues to mitigate the risk of surgery. There have been new clinical trials and discussion on using various chemotherapeutic agents for unresectable, late-stage patients with chondrosarcomas, as well as those with dedifferentiated or mesenchymal chondrosarcomas[9]. Our study supports increased trial of chemotherapy and radiation in patients not undergoing surgical treatment.

Interestingly, patients with left sided tumors had a higher rate of undergoing surgery. This may likely be secondary to a type I statistical error, however, there are no current studies to date investigating outcomes and laterality in patients with chondrosarcomas. Previous studies have reviewed survival in patients with synovial sarcoma where no difference in overall survival or cancer specific survival was found[10]. Studies outside of limb sarcomas such as retroperitoneal sarcomas have shown patients with left sided solid organ tumors to have increased risk of metastasis but no overall difference in survival[11]. Similar findings were reported in patients with renal cell carcinoma where left sided tumors had increased risk of presenting at an advanced stage, which was thought to be secondary to site specific lymphatic spread – a low probability of concern for metastatic potential in patients with chondrosarcomas[12]. Our study is the first to compare laterality and tendency towards undergoing operative treatment in patients with chondrosarcomas although no direct cause can be detailed at this time and more research is necessary to better understand the relationship. The authors have no explanation at this time for this finding.

Risks for Survival and Mortality

Understanding risks of mortality can help patients better assess treatment options. Developing a proper algorithm to properly stage patients with any malignancy is paramount. Our findings support increasing mortality with higher grade and stage, supporting an intervention protocol for patients with chondrosarcomas pursuing surgical treatment. With a relative resistance to radiation and chemotherapy, surgical treatment has become the mainstay treatment nonetheless various trials are in place for patients unable to undergo surgery. Recent Phase I studies have found favorable results with the use of Ivosidenib, a mutant IDH1 Inhibitor, in patients with advanced chondrosarcomas[13]. Although there are increased adjuvant therapeutics available, our study found that patients who underwent chemotherapy or radiation had an increased risk of mortality. These findings are likely owning to the higher rate of trialing chemotherapy and radiation in unresectable, late-stage chondrosarcomas. However, in our propensity matched analysis, increasing age and nonsurgical treatment were found to be statistically significant increased risk of mortality. Additionally, patients not undergoing operative treatment had a statistically significant decrease in survival time. This follows multiple studies that have also found increased mortality with either nonsurgical treatment of various malignancies[14].

Support for Atypical Cartilaginous Tumors

Low grade (grade 1) chondrosarcomas of long bones are now more commonly known to be called central atypical cartilaginous tumors (ACTs)(15). Chondrosarcomas of the axial skeleton involving flat bones such as the pelvis and scapula are still referred to as Grade 1 chondrosarcomas. ACTs are similar to enchondromas however more aggressive with cortical disruption and less well defined compared to enchondromas. Although the difference between enchondromas and ACTs has been difficult to differentiate recent studies have found PET-CTs and gadolinium enhanced MRIs to be sufficient in differentiating the two[16,17]. With imaging advancements, differentiating between enchondromas and ACTs is

no longer necessary. Although management for these patients has become of increasing discussion given their similarity to enchondromas, it appears that surgeons are continuing to treat them with a biopsy and intralesional excision[18]. In our study, we found the outcome of nonoperative treatment of low grade (grade 1) chondrosarcomas of the long bone or ACTs was not statistically significant to those undergoing operative treatment. This supports the ongoing discussion of ACTs being similarly managed to enchondromas. Previous studies show that this has yet to take place and that surgeons are continuing to treat ACTs more closely to their chondrosarcoma counterparts, however, our research supports that less aggressive measures provide similar mortality outcomes[18].

Limitations

Our study is not without limitations. Although we were able to stratify between patients undergoing surgical and non-surgical treatment for those with chondrosarcomas, we do not have granular data on the reasons for non-surgical treatment. Our study is specific to looking at patients who would have been recommended to undergo surgery but ultimately did not either secondary to a contraindication to surgery or patients refusal for surgery. We understand that decision making in regard to surgery is a multifaceted approach that requires numerous discussions and variables that are not calculated by any database. Understanding the causes for non-operative treatment would help to decipher the population of patients not undergoing surgery which may range from patients refusing and electing to not undergo surgery compared to patients who are unfit for surgery. This study is also limited secondary to some incomplete data in the SEER database - a formal retrospective or prospective study either at a single institution or multi-institutional would help provide data to study the matter in a more targeted manner. Specific prospective studies are required to better understand the different surgical and oncologic treatment options and their outcomes for patients with low grade chondrosarcomas.

CONCLUSIONS

This study provides data to inform the patient on their decisions for or against surgery and may assist the surgeons in counseling patients regarding the surgical treatment of chondrosarcomas. Patients not undergoing operative treatment for chondrosarcomas whether secondary to refusal for surgery or a contraindication to surgery are at statistically significantly increased risk of mortality. Advanced stage was most significantly associated with increased risk of undergoing non-operative treatment. An exception exists for patients with grade 1 chondrosarcoma of the long bone or central atypical cartilaginous tumors for whom no statistical difference was found. This study is limited due to the absence of information in the SEER database describing the reasons for non-operative treatment.

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