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Prognostic Factors of Recurrence and 5-Year Survival in Patients with Conventional Chondrosarcoma and Non-Conventional Variants: A Single Institution Review

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Abstract

Introduction: Age, histological grade, year of diagnosis, tumor location and size, and metastasis were prognostic factors significantly associated with overall survival in patients with chondrosarcoma in several nationwide database studies. However, most single institutional studies regarding to prognostic factors addressed on conventional chondrosarcoma exclusively. Few investigate the differences of prognostic factors between conventional type and nonconventional variants. We conducted this study to identify the factors exerting a negative effect on recurrence and 5-year survival.

Materials and methods: We retrospectively enrolled 55patients who were pathologically diagnosed with chondrosarcoma between January 1998 and July 2016. Demographics, namely sex, age at diagnosis, conventional or non-conventional variants, tumor size and location, histological grade, treatment including surgery and adjuvant chemotherapy were reviewed. Using univariate logistic regression analysis to identify independent risk variables for recurrence and survival outcomes.

Results: Fifty-fifth patients pathologically diagnosed chondrosarcoma were divided into conventional and non-conventional variants, with 44 and 11 patients respectively. In univariate logistic regression model of conventional subgroup, wide tumor excision showed protective effect both in recurrence and 5-year survival, compared to marginal resection. Additionally, age at diagnosis and high-grade were negative prognostic factors only in survival outcome. None factor was found relevant in non-conventional variants.

Conclusion: Surgical intervention is a mainstay strategy for chondrosarcoma treatment. Wide tumor excision provides protective effect in recurrence and 5-year survival for patients with conventional type, but not in non-conventional variants.

Keywords: Chondrosarcoma; Prognostic factors; Local recurrence; 5-year survival

Introduction

Chondrosarcomas constitute a heterogeneous group of malignant bone neoplasms with hyaline cartilage differentiation. They are the second most common bone malignancy (after osteosarcoma), accounting for approximately 20% of bone sarcomas, and may occur at any age between 10 and 80 years, mostly during middle age [1]. Prognostic factors of chondrosarcoma have been revealed from single institute and nationwide registry studies. Poor prognostic factors included pelvic lesions, higher tumor grade, metastatic disease, and age were concluded from a university hospital in Germany [2]. The Netherlands Cancer Registry study [3] demonstrated that the prognostic factors significantly associated with overall survival were age, histological grade, year of diagnosis, tumor location, and tumor size, although the efficacy of curettage could not be proven. Two studies conducted using the Cancer Registry of Norway concluded that soft tissue component, age at diagnosis, and metastasis at diagnosis were poor prognostic

factors of disease-specific survival, and that local recurrence was associated with a significantly increased risk of metastasis and death overall [4,5].The survival analysis based on the United States Surveillance, Epidemiology, and End Results (SEER) database identified age, histological grade, year of diagnosis, tumor location and size, and metastasis (AJCC stage IV) as prognostic factors significantly associated with overall survival [6]. Owning to these sarcomas (in conventional and in most non-conventional variants) are resistant to both chemotherapy and radiation, and the only effective therapy currently available is wide local excision—a challenging procedure for surgical oncologists. Only few studies have validated the influence of surgical intervention on survival of patients with conventional chondrosarcoma [7-9]. This retrospective study aimed to identify the prognostic factors of local recurrence and 5-year survival outcomes in chondrosarcoma patients regarding to demographics, tumor characteristics and treatment regimens including surgical modalities and adjuvant chemotherapy.

Materials and Methods

We analyzed the database of National Taiwan University Hospital (NTUH), a tertiary referral hospital in Taiwan by collaboration with the Department of Medical Research at NTUH to conduct this study. Using the NTUH Integrated Medical Database, we retrieved relevant items from electronic medical records of patients who were pathologically diagnosed with chondrosarcoma between January 1998 and July 2016. The following data were collected: sex, age on diagnosis, tumor size (maximum dimension) and location (soft tissue, axial skeleton, appendicular skeleton), histological subtypes and pathological grading, treatment modalities including surgical intervention (wide tumor excision, marginal resection and intralesional curettage) and adjuvant chemotherapy. Wide Tumor Excision (WTE) was defined as the tumor lesions were excised with a rim of healthy tissue. In contrast to WTE, marginal resection involved an intact tumor capsule but suspicious contamination. Intralesional curettage was usually carried out by weighting the balance between tumor eradication and functional preservation. We reviewed all types of chondrosarcoma and categorized them as conventional and non-conventional subgroups with low- or high-grade according to pathological examination. Surgical interventions and adjuvant chemotherapy as treatment modalities were also analyzed. Two conditions of outcomes were defined as recurrence (local recurrence with or without distant metastasis) and 5-year survival. We excluded distant metastasis at diagnosis which clearly causes poor survival. Statistical assessment: Independent t test and chi-square test were used to identify the prognostic factors affecting on local recurrence and survival outcomes. SAS 9.4 (SAS, Cary, NC, USA) was used to analyze data for the univariate logistic regression models. The differences were considered valid at $p < 0.05$.

Results

Eligible fifty-fifth patients, pathologically diagnosed chondrosarcoma, were divided into conventional and non-conventional variants, with 44 and 11 patients respectively. Among conventional subgroup, 34 were men and 10 were women, with a sex ratio of 3.4:1. The mean age at diagnosis was 46.4 ± 17.3 years. Five-year survival rate was 70.5% and recurrence rate was 40.9%. Surgery and adjuvant chemotherapy were statistically significant factors of recurrence **(Table 1).** Neither tumor size nor tumor location was relevant. For 5-year survival outcome, age at diagnosis, histological grade, surgery and adjuvant chemotherapy were identified as prognostic factors **(Table 2).** In univariate logistic regression model **(Table 3),** surgical Wide Tumor Excision (WTE) had protective effect compared to marginal resection regarding to occurrence (OR = 0.011, 95% CI < 0.001-0.143, p < 0.05) and 5-year survival (OR = 0.045, 95% CI, 0.004-0.48, p < 0.05), but no outcome differences between intralesional curettage and marginal resection. Additionally, age at diagnosis and high-grade were negative prognostic factors only in 5-year survival outcome. Adjuvant chemotherapy implying poor prognosis reflected the fact that chondrosarcomas were with chemoresistance. In non-conventional variants, 5 were men and 6 were women with mean age 50.3 ± 21.9 years. Five-year survival rate was 27.3% and recurrence rate was 72.7%. None factor was found relevant in non-conventional variants.

Table 1: Prognostic factors of recurrence in conventional and in non-conventional chondrosarcoma.

Outcome 1 Recurrence	Conventional (n=44)					Non-conventional (n=11)				
	Yes		No			Yes		No		
	n	(%)	n	(%)	p value	n	(%)	n	(%)	p value
Patient No.	(n=18)		(n=26)			(n=8)		(n=3)		
Age, mean (SD)	49.56	-18.77	44.35	-16.29	0.3327	46.75	-20.47	60	-27.22	0.3999
Sex, (%)					0.947					1
Male	14	-77.78	20	-76.92		4	-50	1	-33.33	
Female	4	-22.22	6	-23.08		4	-50	2	-66.67	

Tumor size, (%)					0.7631					1
<10 cm	11	-68.75	19	-73.08		5	-62.5	2	-66.67	
>=10cm	5	-31.25	7	-26.92		3	-37.5	1	-33.33	
Location, (%)					1					0.5152
Soft tissue	0	0	0	0		4	-50	1	-33.33	
Axial skeleton	9	-50	13	-50		2	-25	2	-66.67	
Appendicular skeleton	9	-50	13	-50		2	-25	0	0	
Grade, (%)					0.772					NA
I/Low	7	-38.89	9	-34.62		0	0	0	0	
II/High	11	-61.11	17	-65.38		8	-100	3	-100	
Surgery, (%)					**0**					0.4061
Wide Tumor Excision (WTE)	1	-5.56	22	-84.62		1	-12.5	2	-66.67	
Marginal Resection (MR)	8	-44.44	2	-7.69		6	-75	1	-33.33	

Intralesional Curettage (IC)	9	-50	2	-7.69		1	-12.5	0	0	
Chemotherapy, (%)	14	-77.78	9	-34.62	**0.0048**	5	-62.5	1	-33.33	0.5455

Table 2: Prognostic factors of 5-year survival in conventional and in non-conventional chondrosarcoma.

Outcome 2 5-year survival	Conventional (n=44)					Non-conventional (n=11)				
	Yes		No			Yes		No		
	n	(%)	n	(%)	p value	n	(%)	n	(%)	p value
Patient No.	(n=13)		(n=31)			(n=8)		(n=3)		
Age, mean (SD)	41.42	-14.98	58.54	-17.06	**0.0019**	53.33	-19.35	49.25	-23.94	0.7991
Sex, (%)					0.9714					1
Male	24	-77.42	10	-76.92		1	-33.33	4	-50	
Female	7	-22.58	3	-23.08		2	-66.67	4	-50	
Tumor size, (%)					0.6657					0.2364
<10 cm	22	-73.33	8	-66.67		3	-100	4	-50	

>=10cm	8	-26.67	4	-33.33		0	0	4	-50	
Location, (%)					0.3216					0.2121
Soft tissue	0	0	0	0		0	0	5	-62.5	
Axial skeleton	17	-54.84	5	-38.46		2	-66.67	2	-25	
Appendicular skeleton	14	-45.16	7	-61.54		1	-33.33	1	-12.5	
Grade, (%)					**0.0151**					NA
I/Low	15	-48.39	1	-7.69		0	0	0	0	
II/High	16	-51.61	12	-92.31		3	-100	8	-100	
Surgery, (%)					**0.0002**					0.4061
Wide Tumor Excision (WTE)	22	-70.97	1	-7.69		1	-33.33	2	-25	
Marginal Resection (MR)	5	-16.13	5	-38.46		1	-33.33	6	-75	
Intralesional Curettage (IC)	4	-12.9	7	-53.85		1	-33.33	0	0	
Chemotherapy, (%)	13	-76.92	10	-41.94	**0.034**	2	-66.67	4	-50	1

Table 3: The potential risk factors associated with recurrence or 5-year survival in conventional chondrosarcoma patients.

	Odd Ratio (95% CI)	p value
Outcome 1. Recurrence		
Surgery (WTE vs. MR)	**0.011** (<0.001 – 0.143)	**0.0005**
Surgery (IC vs. MR)	1.125 (0.127 – 9.943)	0.9156
Chemotherapy (Yes vs. No)	6.611 (1.673 – 26.117)	**0.0071**
Outcome 2. 5-year survival		
Age at diagnosis	1.070 (1.019 – 1.1124)	**0.0065**
Grade (High vs. Low)	11.249 (1.3 – 97.362)	**0.0279**
Surgery (WTE vs. MR)	**0.045** (0.004 – 0.48)	**0.0101**
Surgery (IC vs. MR)	1.750 (0.306 – 10.022)	0.5297
Chemotherapy (Yes vs. No)	4.615 (1.057 – 20.158)	**0.0420**

Discussion

Chondrosarcoma is the second most common skeletal malignancy, and its treatment requires a multidisciplinary approach involving medical, surgical, and radiation oncologists **[1].** Demographic and prognostic factors associated with chondrosarcoma in Scandinavian countries **[3-5]** and the United States [6] are well documented. Owning to the sarcomas resisted to both chemotherapy and radiation, making wide local excision the only therapy proven to be effective **[1].** Chen et al. **[9]** investigated the prognostic factors and survival in conventional chondrosarcoma in Taiwanese population showed the surgical margins were statistically associated with the risk of subsequent local recurrence but did not predict survival. The development of distant metastases was an independent prognostic factor for poor survival. To address the lack of local data and to validate surgical effects in survival, we reviewed an 18-year database of a tertiary medical center in north Taiwan. A total of 55 patients were enrolled retrospectively and was divided into conventional and non-conventional subgroup. Most of the patients in conventional type were men and in their middle years, but sex equally was found in non-conventional type. In conventional subgroup, the majority of the tumors involved the extremities as described in Western and local studies **[3,4,6,9].** The 5-year

survival rate was 70.5%and recurrence rate was 40.9%. In concordance with previous study [6], patients with older age and with poorly differentiated grading exhibited inferior survival. Regarding to treatment modalities, we found surgical Wide Tumor Excision (WTE) provides protective effect compared to marginal resection regarding to occurrence and 5-year survival, but no outcome differences between intralesional curettage and marginal resection. Our findings were in consistent with Chen et al. [9] reported local recurrence might influence survival and two studies based on the Cancer Registry of Norway, the researchers concluded that local recurrence was associated with a significantly increased risk of metastasis and death overall [4,5]. On the other hand, Fromm et al. [2] observed that margin status influenced local recurrence free survival, but not overall survival. One systematic review concluded that intralesional resection for central grade 1 chondrosarcoma yields lower complications and superior functional outcomes, with no significant increase in the risk of recurrence and metastasis [7]. Another case-series study suggested extended curettage for central low-grade chondrosarcoma to reduce soft tissue damage and surgical risk [8]. Careful judgment and shared decision making must be exercised to make balance between radical resection for optimal survival and functional preservation.

With microsurgery, reconstructive plastic surgeons may help to not only improve limb salvage rates but also create wider margins without altering the oncologic goals of curative resection [10]. In a retrospective study conducted at Duke University Medical Center from 2001 to 2014, 116 of 747 patients with skeletal and soft tissue sarcoma underwent reconstructive surgery [11]. The study revealed that tumor location was associated with the need for surgical reconstruction in patients with upper or lower extremity tumors, a history of operative interventions, and neoadjuvant radiotherapy. We recruited three reconstructive plastic surgeons may enhance the care coordination at the multidisciplinary sarcoma center and improved outcomes, including rates of limb salvage, functionality, and esthetic results. This may have led to a slightly lower recurrence rate (40.9%) in our study than in the study of Chen et al. (52.7%) [9]. In this study, we tried to find the prognostic factors in non-conventional subgroup, 4 patients with Extra Skeletal Myxoid Chondrosarcoma (EMCS) and 7 with Mesenchymal Chondrosarcoma (MCS), are very rare malignant soft tissue sarcomas. None factor was found relevant in non-conventional variants. Although chemotherapy showed negative impacts in recurrence and survival outcomes in conventional chondrosarcoma patients, we interpreted it as salvage therapy after marginal resection or intralesional curettage. We recognized current chemotherapy has no survival benefits in both subgroups.

Survival prediction models developed on the basis of the United States SEER registry have transformed surgical care delivery, including nomograms, which assist clinicians in precisely estimating a patient's likelihood of survival [12,13], and the Skeletal Oncology Research Group's algorithms(https://sorg-apps.shinyapps.io/chondrosarcoma), artificial intelligence, machine learning, and big data [14,15] was introduced as well. These prediction models could assist personalized prognostic evaluation and individualized clinical decision-making. Further external validation and native nationwide survey are necessary. There were several limitations to this study. First, this was a retrospective study, and many variables could not be controlled. Therefore, we did not perform survival analysis but rather used logistic regression models. Second, our sample was small. The incidence of chondrosarcoma in Norway is 2.85–3.45/million/year [4], and the previous Taiwanese study identified only 55 patients during a 14-year-

period **[9].** Despite the low incidence of chondrosarcoma, a high fatality rate was observed in high-grade cases and attention must be paid. Third, adjuvant chemotherapy was not comprehensively studied, although it did not significantly affect survival. Novel regimens have been widely investigated, and they may benefit survival **[16-18].** Future database establishment involving multicenter collaboration or a national registry are obligated.

Conclusions

Surgical intervention is a mainstay strategy for chondrosarcoma treatment. Wide tumor excision provides protective effect in recurrence and 5-year survival for patients with conventional type, but not in non-conventional variants. We also emphasized the role of reconstructive plastic surgeons in ensuring adequate oncological safety margin during resection so that any defects could be reconstructed and functionality restored.

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