Prognosis and treatment differences between initial and second primary chondrosarcoma

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Abstract. Prognosis and treatment differences between initial and second primary chondrosarcoma (pCS) remain unknown. In the present study, patients with chondrosarcoma diagnosed between January 2004 and December 2015 were identified using the Surveillance Epidemiology and End Results database. Kaplan-Meier curves and log-rank tests were used to assess overall survival (OS) and cancer-specific survival. Univariable and multivariable Cox regression analyses were used to determine factors associated with all-cause mortality and cancer-specific mortality. In total, 1,655 eligible patients were included in the cohort of the present study, of which, 1,455 (87.9%) had initial pCS and 200 (12.1%) had second pCS. Patients with second pCS were more frequently diagnosed in the age range of 61-80 years compared with patients with initial pCS (52.5 vs. 43.1%; P<0.001). The OS rate of patients with initial pCS was significantly higher than that of patients with second pCS (78.3 vs. 63.0%; P<0.001). Multivariable logistic regression analyses suggested that second pCS predicted higher all-cause mortality (hazard ratio, 1.72; 95% confidence interval, 1.31-2.26, P<0.001) compared with that in patients with initial pCS. Furthermore, there were no differences observed in the treatment benefits between the patients with initial and second pCS. In conclusion, second pCS was more frequently diagnosed in older patients compared with initial pCS. In addition, the prognosis of patients with second pCS was worse than that of patients with initial pCS, and the treatment is essentially the same for initial and second pCS.

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Introduction

Chondrosarcoma is a malignant tumour originating from cartilage tissue and is the second most common malignant bone tumour after osteosarcomas worldwide (1,2). Chondrosarcoma primarily occurs in individuals >50 years of age and, in the majority of cases, affects the limbs and pelvis (3). Pathological types can be divided into conventional intramedullary chondrosarcoma, clear cell chondrosarcoma, mesenchymal chondrosarcoma, juxtacortical chondrosarcoma and myxoid chondrosarcoma (4,5). Chondrosarcoma has a poor response to traditional chemotherapy and radiotherapy, and surgical resection is currently the only successful treatment available (6-8).

In recent years, second primary cancer types have become more prominent, and the incidence and risk of second primary cancer is increasing in countries such as the USA and the Netherlands (9,10). This increase may be due to a significant improvement in the survival times of those adults with cancer or the use of commonly used cancer treatments such as radiotherapy or chemotherapy (11-13). In the present study, second primary chondrosarcoma (pCS) is defined as a tumour that is different in location or histology from the initial pCS and is not derived from the metastasis or recurrence of the initial pCS. Chondrosarcoma rarely presents as a second primary tumour (10).

To the best of our knowledge, no studies have evaluated the prognosis or treatment differences between the initial pCS and the second pCS thus far. The purpose of the present study was to analyse the difference in prognosis between the initial and second pCS, and the difference in treatment outcomes on the basis of a population-level study of chondrosarcoma.

Materials and methods

Data source and patients. The Surveillance Epidemiology and End Results (SEER) database (https://seer.cancer.gov/) of the National Cancer Institute (Bethesda, MD, USA) was used as the data source in the present study. In total, 3,055 patients with initial and second pCS were identified using the International Classification of Diseases for Oncology (ICD-O-3) (http://codes.iarc.fr/) histology codes 9220/3,9221/3,9231/3,9240/3,9242/3 and 9243/3. The patients had

been diagnosed between January 1, 2004, and December 31, 2015. SEER*Stat software (version 8.3.5; National Cancer Institute) was used to access the SEER 18 Regs Custom Data (with an additional treatment field) Nov 2017 Sub (1973-2015 varying) database using the client-server mode of SEER*Stat. Patients with unknown survival time, unknown American Joint Committee on Cancer (AJCC) stage or unknown Tumour-Node-Metastasis (TNM) stage (14), as well as those diagnosed at autopsy, <18 years of age or having a non-initial visit to hospital and non-osteoarticular chondrosarcoma were excluded. The National Cancer Institute's SEER database covers ~30% of the population in the USA, and collects information such as demographics, tumour histology, tumour stage at diagnosis, treatment information and survival time (15). Finally, 1,655 eligible patients were identified.

The second pCS may be synchronous or metachronous. The definitions of the second pCS met the following criteria: i) Synchronous cancer is a second pCS diagnosed simultaneously or within 6 months of diagnosis of the initial pCS (9); ii) metachronous cancer is a diagnosis of second pCS ≥6 months following the diagnosis of an initial pCS; iii) the primary site differs between the initial pCS and the second pCS; iv) histology is different if the primary site is the same as the primary site of the initial primary cancer.

Study variables. Overall survival (OS) and cancer-specific survival (CSS) were the primary outcomes in the present study. The patients in the present study were categorized into two groups: Initial pCS and second pCS. The following variables were extracted for analysis: Year of diagnosis, age at diagnosis, sex, ethnicity, marital status, area of geographical state, urban-rural residence, laterality, primary site, tumour grade, histological type, AJCC stage, extent of disease (for T and M stages), regional nodes positive (for N stage) and treatment methods (surgery, radiotherapy or chemotherapy).

Statistical analysis. The baseline data of demographics and clinicopathological characteristics of the initial and second pCS were compared using χ^2 tests. Kaplan-Meier curves and log-rank tests were used for OS and CSS. Univariable analysis was performed using the log-rank test to determine the factors associated with all-cause mortality and cancer-specific mortality. Furthermore, univariable and multivariable Cox regression analyses were used to determine the factors associated with all-cause mortality and cancer-specific mortality. All statistical analyses were performed using SPSS statistics software (version 20; IBM Corp., Armonk, NY, USA). $P \leq 0.05$ was considered to indicate a statistically significant result.

Results

Demographic and clinical characteristics of the initial and second pCS. In total, 1,655 eligible patients with chondrosarcoma who were diagnosed between January 1, 2004, and December 31, 2015, were included in the cohort of the present study, with data obtained from the SEER database between January 1, 2004, and December 31, 2015. Among them, 1,455 (87.9%) patients had initial pCS and 200 (12.1%) patients had second pCS. The clinical characteristics and the χ^2 test for comparison of the initial and second pCS are presented in Table I. The data presented in Table I indicates that the incidence of chondrosarcoma increases with the year of diagnosis. χ^2 test revealed significant differences between the initial and second pCS in certain variables, including year of diagnosis (P=0.048), age at diagnosis (P<0.001), tumour AJCC stage (P=0.024) and M-stage (P=0.044). Patients with second pCS were more frequently diagnosed at 61-80 years of age (52.5 vs. 43.1%; P<0.001) compared with patients with initial pCS. Furthermore, the majority of patients with initial and second pCS chose to receive surgical treatment (92.0 and 91.0% respectively), and markedly less patients chose to receive radiotherapy (14.8 and 15.0%, respectively) or chemotherapy (8.0 vs. 5.5%, respectively).

Univariate survival analyses of factors associated with all-cause mortality and cancer-specific mortality. Univariate survival analyses of patients with initial and second pCS according to various clinicopathological variables (Table II). Among the 1,655 initial and second pCS patients, 390 (23.6%) were categorized as cases of all-cause mortality and 228 (13.8%) succumbed to chondrosarcoma. Univariate analyses revealed that year of diagnosis, age at diagnosis, sex, tumour grade, histological type, AJCC stage, TNM stage, surgery, radiotherapy and chemotherapy were associated with all-cause mortality and chondrosarcoma-associated mortality (all P<0.05). In addition, patients with second pCS had a higher rate of all-cause mortality compared with patients with initial pCS (P<0.001), but there was no significant difference between initial and second pCS in terms of chondrosarcoma-associated mortality (P=0.734).

Survival. The median survival time among the entire cohort was 41.00 months, with patients with initial pCS experiencing a longer median survival time (42.00 months), and patients with second pCS experiencing a shorter median survival time (34.50 months). Fig. 1A presents the OS and CSS of the initial and second pCS. The OS rate of patients with initial pCS was significantly higher compared with that of the patients with second pCS (log-rank test, P<0.001), but the CSS rate of the patients with initial pCS was not significantly different from that of the patients with second pCS (log-rank test, P=0.428). In addition, it was also revealed that among the pathological types of chondrosarcoma, dedifferentiated chondrsarcoma exhibited the worst OS and CSS rates (Fig. 1B). Patients were stratified by primary sites and laterality, and in doing so, it was revealed that the OS rate of the patients with initial pCS was also higher compared with that of the patients with second pCS. However, there was no significant difference between the initial and second pCS in terms of chondrosarcoma-associated mortality (Fig. 2).

Risk factors for all-cause mortality and cancer-specific mortality. Univariate and multivariate Cox regression were used to analyse the factors associated with all-cause mortality and cancer-specific mortality (Table III). Age at diagnosis, sex, histological type, AJCC stage, T stage, surgery and radiotherapy were associated with all-cause mortality and chondrosarcoma-cause mortality (all P<0.05) in univariate and multivariate Cox regression. In the multivariate Cox regression analysis among patients with initial and second pCS, age

Table I. Characteristics of patients stratified by initial and second pCS.

Characteristics	All patients	Initial pCS	Second pCS	P-value
Total, n (%)	1,655	1,455 (87.9)	200 (12.1)	
Median survival, months	41.00	42.00	34.50	
Year of diagnosis, n (%)				0.048
2004-2006	343 (20.7)	299 (20.5)	44 (22.0)	
2007-2009	399 (24.1)	363 (24.9)	36 (18.0)	
2010-2012	427 (25.8)	362 (24.9)	65 (32.5)	
2013-2015	486 (29.4)	431 (29.6)	55 (27.5)	
Age at diagnosis in years, n (%)				<0.001
18-40	392 (23.7)	382 (26.3)	10 (5.0)	
41-60	691 (41.8)	627 (43.1)	64 (32.0)	
61-80	490 (29.6)	385 (26.5)	105 (52.5)	
>80	82 (5.0)	61 (4.2)	21 (10.5)	
Sex, n (%)				0.724
Female	742 (44.8)	650 (44.7)	92 (46.0)	
Male	913 (55.2)	805 (55.3)	108 (54.0)	
Ethnicity, n (%)				0.882
Caucasian	1,444 (87.3)	1,269 (87.2)	175 (87.5)	
African-American	111 (6.7)	99 (6.8)	12 (6.0)	
Other	100 (6.0)	87 (6.0)	13 (6.5)	
Marital status, n (%)				0.265
Married	957 (57.8)	831 (57.1)	126 (63.0)	
Single	622 (37.6)	555 (38.1)	67 (33.5)	
Unknown	76 (4.6)	69 (4.7)	7 (3.5)	
State, n (%)				0.751
West	875 (52.9)	763 (52.4)	112 (56.0)	
Northeast	300 (18.1)	267 (18.4)	33 (16.5)	
South	334 (20.2)	294 (20.2)	40 (20.0)	
Midwest	146 (8.8)	131 (9.0)	15 (7.5)	
Urban-rural residence, n (%)				0.650
Metropolitan	1,472 (88.9)	1,296 (89.1)	176 (88.0)	
Non-metropolitan	183 (11.1)	159 (10.9)	24 (12.0)	
Laterality, n (%)				0.907
Left	633 (38.2)	554 (38.1)	79 (39.5)	
Right	676 (40.8)	597 (41.0)	79 (39.5)	
Other	346 (20.9)	304 (20.9)	42 (21.0)	
Primary site, n (%)				0.542
Appendicular	803 (48.5)	710 (48.8)	93 (46.5)	
Axial	852 (51.5)	745 (51.2)	107 (53.5)	
Grade, n (%)				0.505
Well-differentiated	575 (34.7)	513 (35.3)	62 (31.0)	
Moderately differentiated	684 (41.3)	603 (41.5)	81 (40.5)	
Poorly differentiated	230 (13.9)	198 (13.6)	32 (16.0)	
Undifferentiated	141 (8.5)	119 (8.2)	22 (11.0)	
Unknown	25 (1.5)	22 (1.5)	3 (1.5)	
Histological type, n (%)				0.633
Chondrosarcoma, NOS	1,353 (81.8)	1,191 (81.9)	162 (81.0)	
Juxtacortical chondrosarcoma	21 (1.3)	19 (1.3)	2 (1.0)	
Myxoid chondrosarcoma	102 (6.2)	93 (6.4)	9 (4.5)	
Mesenchymal chondrosarcoma	18 (1.1)	16 (1.1)	2 (1.0)	
Clear cell chondrosarcoma	11 (0.7)	10 (0.7)	1 (0.5)	
Dedifferentiated chondrosarcoma	150 (9.1)	126 (8.7)	24 (12.0)	

Table I. Continued.

Characteristics	All patients	Initial pCS	Second pCS	P-value
AJCC stage, n (%)				0.024
I	1,213 (73.3)	1,072 (73.7)	141 (70.5)	
II	307 (18.5)	257 (17.7)	50 (25.0)	
III	18 (1.1)	16 (1.1)	2 (1.0)	
IV	117 (7.1)	110 (7.6)	7 (3.5)	
T-stage, n (%)				0.593
T1	1,020 (61.6)	903 (62.1)	117 (58.5)	
T2	608 (36.7)	528 (36.3)	80 (40.0)	
T3	27 (1.6)	24 (1.6)	3 (1.5)	
N-stage, n (%)				0.359
N0	1,636 (98.9)	1,437 (98.8)	199 (99.5)	
N1	19 (1.1)	18 (1.2)	1 (0.5)	
M-stage, n (%)				0.044
M0	1,552 (93.8)	1,358 (93.3)	194 (97.0)	
M1	103 (6.2)	97 (6.7)	6 (3.0)	
Surgery, n (%)				0.617
No	134 (8.1)	116 (8.0)	18 (9.0)	
Yes	1,521 (91.9)	1,339 (92.0)	182 (91.0)	
Radiotherapy, n (%)				0.934
No	1,410 (85.2)	1,240 (85.2)	170 (85.0)	
Yes	245 (14.8)	215 (14.8)	30 (15.0)	
Chemotherapy, n (%)				0.207
No	1,527 (92.3)	1,338 (92.0)	189 (94.5)	
Yes	128 (7.7)	117 (8.0)	11 (5.5)	

Percentages may not total 100 due to rounding. AJCC, American Joint Committee on Cancer; pCS, primary chondrosarcoma; NOS, not otherwise specified.

41-60 years [vs. age 18-40 years; HR, 1.80; 95% confidence interval (CI), 1.22-2.65; P=0.003], age 61-80 years (vs. age 18-40 years; HR, 2.91; 95% CI, 1.97-4.30; P<0.001), age >80 years (vs. age 18-40 years; HR, 4.04; 95% CI, 2.49-6.57; P<0.001), male (vs. female; HR, 1.50; 95% CI, 1.21-1.85; P<0.001), moderately differentiated (vs. well-differentiated; HR, 1.41; 95% CI, 1.03-1.93; P=0.033), undifferentiated (vs. well-differentiated; HR, 2.00; 95% CI, 1.09-3.68; P=0.026), mesenchymal chondrosarcoma (vs. chondrosarcoma, NOS; HR, 2.11; 95% CI, 1.03-4.33; P=0.042), dedifferentiated chondrosarcoma (vs. chondrosarcoma, NOS; HR, 3.00; 95% CI, 2.20-4.08; P<0.001), AJCC stage IV (vs. AJCC stage I; HR, 5.67; 95% CI, 3.64-8.82; P<0.001), T2 stage (vs. T1 stage; HR, 1.81; 95% CI, 1.46-2.25; P<0.001), surgery (vs. no surgery; HR, 0.39; 95% CI, 0.29-0.52; P<0.001), radiotherapy (vs. no radiotherapy; HR, 1.31; 95% CI, 1.03-1.67; P=0.030) and second pCS (vs. initial pCS; HR, 1.72; 95% CI, 1.31-2.26; P<0.001) were associated with a significant increase in all-cause mortality. However, initial and second pCS were still not associated with improved chondrosarcoma-associated survival on multivariable survival analysis (P=0.294).

Benefits of different treatment for initial and second pCS. To analyse the benefit of different treatments for all-cause mortality, patients with initial and second pCS were stratified by primary site and laterality, and multivariate analysis was used. For patients with appendicular or axial chondrosarcoma, those with initial and second pCS who underwent surgery had lower all-cause mortality (all P<0.05; Fig. 3A) compared with patients who did not receive surgery (Fig. 3A). Similarly, for left-sided or right-sided chondrosarcoma patients, those with initial and second pCS who underwent surgery had lower all-cause mortality rate (all P<0.05) compared with patients without surgery. However, the use of radiotherapy or chemotherapy did not reduce the all-cause mortality rate (Fig. 3B and C).

Discussion

The incidence of chondrosarcoma accounts for ~20% of all primary bone sarcomas (16). Above the age of 40 years, the incidence rate of chondrosarcoma gradually increases, and the incidence rate in men is higher than that in women. Rozeman *et al* (17) reported that common types of chondrosarcoma accounted for 85% of cases, dedifferentiation for 10%, interstitial type for 2% and clear cell type for 1%. Giuffrida *et al* (18) analysed 2,890 cases of chondrosarcoma between 1973 and 2003, and revealed that the highest 5-year survival rate was that of clear cell type chondrosarcoma

Table II. Univariate survival analyses of the 1,655 patients with chondrosarcoma according to various clinicopathological variables.

	All-cause			Chondrosarcoma-associated		
Characteristics	Succumbed, n (%)	Alive, n (%)	P-value	Succumbed, n (%)[a]	Censored, n (%)	P-value
Total patients in study	390 (23.6)	1,265 (76.4)		228 (13.8)	1,427 (86.2)	
Year of diagnosis			<0.001			<0.001
2004-2006	120 (30.8)	223 (17.6)		68 (29.8)	275 (19.3)	
2007-2009	109 (27.9)	290 (22.9)		62 (27.2)	337 (23.6)	
2010-2012	109 (27.9)	318 (25.1)		69 (30.3)	358 (25.1)	
2013-2015	52 (13.3)	434 (34.3)		29 (12.7)	457 (32.0)	
Age at diagnosis, years			<0.001			<0.001
18-40	38 (9.7)	354 (28.0)		27 (11.8)	365 (25.6)	
41-60	142 (36.4)	549 (43.4)		92 (40.4)	599 (42.0)	
61-80	167 (42.8)	323 (25.5)		93 (40.8)	397 (27.8)	
>80	43 (11.0)	39 (3.1)		16 (7.0)	66 (4.6)	
Sex			<0.001			0.041
Female	144 (36.9)	598 (47.3)		88 (38.6)	654 (45.8)	
Male	246 (63.1)	667 (52.7)		140 (61.4)	773 (54.2)	
Ethnicity			0.390			0.862
Caucasian	339 (86.9)	1,105 (87.4)		201 (88.2)	1,243 (87.1)	
African-American	31 (7.9)	80 (6.3)		15 (6.6)	96 (6.7)	
Other	20 (5.1)	80 (6.3)		12 (5.3)	88 (6.2)	
Marital status			0.352			0.491
Married	220 (56.4)	737 (58.3)		135 (59.2)	822 (57.6)	
Single	156 (40.0)	466 (36.8)		86 (37.7)	536 (37.6)	
Unknown	14 (3.6)	62 (4.9)		7 (3.1)	69 (4.8)	
State			0.469			0.309
West	209 (53.6)	666 (52.6)		129 (56.6)	746 (52.3)	
Northeast	65 (16.7)	235 (18.6)		35 (15.4)	265 (18.6)	
South	75 (19.2)	259 (20.5)		40 (17.5)	294 (20.6)	
Midwest	41 (10.5)	105 (8.3)		24 (10.5)	122 (8.5)	
Urban-rural residence			0.836			0.684
Metropolitan	348 (89.2)	1,124 (88.9)		201 (88.2)	1,271 (89.1)	
Non-metropolitan	42 (10.8)	141 (11.1)		27 (11.8)	156 (10.9)	
Laterality			0.941			0.224
Left	152 (39.0)	481 (38.0)		94 (41.2)	539 (37.8)	
Right	158 (40.5)	518 (40.9)		96 (42.1)	580 (40.6)	
Other	80 (20.5)	266 (21.0)		38 (16.7)	308 (21.6)	
Primary site			0.887			0.532
Appendicular	188 (48.2)	615 (48.6)		115 (50.4)	688 (48.2)	
Axial	202 (51.8)	650 (51.4)		113 (49.6)	739 (51.8)	
Grade			<0.001			<0.001
Well-differentiated	61 (15.6)	514 (40.6)		26 (11.4)	549 (38.5)	
Moderately differentiated	133 (34.1)	551 (43.6)		76 (33.3)	608 (42.6)	
Poorly differentiated	87 (22.3)	143 (11.3)		56 (24.6)	174 (12.2)	
Undifferentiated	89 (22.8)	52 (4.1)		60 (26.3)	81 (5.7)	
Unknown	20 (5.1)	5 (0.4)		10 (4.4)	15 (1.1)	
Histological type			<0.001			<0.001
Chondrosarcoma, NOS	242 (62.1)	1,111 (87.7)		137 (60.1)	1,216 (85.2)	
Juxtacortical chondrosarcoma	2 (0.5)	19 (1.5)		2 (0.9)	19 (1.3)	
Myxoid chondrosarcoma	29 (7.4)	73 (5.8)		20 (8.8)	82 (5.7)	
Mesenchymal chondrosarcoma	10 (2.6)	8 (0.6)		7 (3.1)	11 (0.8)	
Clear cell chondrosarcoma	3 (0.8)	8 (0.6)		0 (0.0)	11 (0.8)	
Dedifferentiated chondrosarcoma	104 (26.7)	46 (3.6)		62 (27.2)	88 (6.2)	

Table II. Continued.

	All-cause			Chondrosarcoma-associated		
Characteristics	Succumbed, n (%)	Alive, n (%)	P-value	Succumbed, n (%)[a]	Censored, n (%)	P-value
AJCC stage			<0.001			<0.001
I	164 (42.1)	1,049 (82.9)		75 (32.9)	1,138 (79.7)	
II	126 (32.3)	181 (14.3)		78 (34.2)	229 (16.0)	
III	6 (1.5)	12 (0.9)		3 (1.3)	15 (1.1)	
IV	94 (24.1)	23 (1.8)		72 (31.6)	45 (3.2)	
T-stage			<0.001			<0.001
T1	151 (38.7)	869 (68.7)		80 (35.1)	940 (65.9)	
T2	226 (57.9)	382 (30.2)		141 (61.8)	467 (32.7)	
T3	13 (3.3)	14 (1.1)		7 (3.1)	20 (1.4)	
N-stage			<0.001			<0.001
N0	378 (96.9)	1,258 (99.4)		220 (96.5)	1,416 (99.2)	
N1	12 (3.1)	7 (0.6)		8 (3.5)	11 (0.8)	
M-stage			<0.001			<0.001
M0	304 (77.9)	1,248 (98.7)		161 (70.6)	1,391 (97.5)	
M1	86 (22.1)	17 (1.3)		67 (29.4)	36 (2.5)	
Surgery			<0.001			<0.001
No	74 (19.0)	60 (4.7)		44 (19.3)	90 (6.3)	
Yes	316 (81.0)	1,205 (95.3)		184 (80.7)	1,337 (93.7)	
Radiotherapy			<0.001			<0.001
No	293 (75.1)	1,117 (88.3)		166 (72.8)	1,224 (87.2)	
Yes	97 (24.9)	148 (11.7)		62 (27.2)	183 (12.8)	
Chemotherapy			<0.001			<0.001
No	308 (79.0)	1,219 (96.4)		170 (74.6)	1,357 (95.1)	
Yes	82 (21.0)	46 (3.6)		58 (25.4)	70 (4.9)	
Group			<0.001			0.734
Initial pCS	316 (81.0)	1,139 (90.0)		202 (88.6)	1,253 (87.8)	
Second pCS	74 (19.0)	126 (10.0)		26 (11.4)	174 (12.2)	

[a]Includes those patients that succumbed to causes other than chondrosarcoma and those that were still alive. Percentages may not total 100 due to rounding. AJCC, American Joint Committee on Cancer; pCS, primary chondrosarcoma; NOS, not otherwise specified; T, tumor; N, node; M, metastasis.

(100%), followed by common chondrosarcoma (70%), and the lowest was that of dedifferentiated chondrosarcoma (0%). The results from the present study also revealed that dedifferentiated chondrosarcoma has the worst prognosis.

Second pCS is a rare occurrence, and, to the best of our knowledge, there are currently no studies that have assessed the prognosis and treatment differences between the initial pCS and the second pCS. Therefore, the present study is the first to report differences in prognosis and treatment between initial pCS and the second pCS.

The present study revealed that the proportion of the four age stages (18-40, 41-60, 61-80 and >80 years) of the patients with initial pCS were 26.3, 43.1, 26.5 and 4.2%, respectively, while the proportion of the patients with second pCS in the four age stages was 5.0,32.0,52.5 and 10.5%, respectively. It was demonstrated that patients with second pCS were at an older age when diagnosed compared with patients with initial pCS. The difference may be due to a significant improvement in survival for patients with cancer.

As one of the multiple primary malignancies (MPMs), the second primary cancer has received greater attention. MPMs are rarely encountered in different organs and tissues in the same patient, and the incidence of MPMs ranges from 0.7-11.0%, as determined through the statistical analysis of several national cancer registries (10,19,20). The most common subsequent types of cancer are squamous cell skin cancer, colorectal cancer and breast cancer (13). Patients with MPMs exhibit a worse 5-year OS rate compared with patients with a single malignancy (21). This may be associated with genetic, environmental and immunological factors, as well as the application of radiotherapy or chemotherapy (22,23).

The risk of developing a subsequent cancer in patients with MPMs was 1.4 to 3.0 times higher compared to the general population (13). There are a number of studies that

Table III. Risk factors for survival: Outcome is all-cause mortality and cancer-specific mortality.

	All-cause mortality				Cancer-specific mortality			
	Univariate Cox regression		Multivariate Cox regression		Univariate Cox regression		Multivariate Cox regression	
Characteristics	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Age at diagnosis, years								
18-40	Reference		Reference		Reference		Reference	
41-60	2.34 (1.63-3.34)	<0.001	1.80 (1.22-2.65)	0.003	2.16 (1.41-3.32)	<0.001	1.86 (1.14-3.02)	0.013
61-80	4.47 (3.14-6.35)	<0.001	2.91 (1.97-4.30)	<0.001	3.77 (2.45-5.78)	<0.001	2.79 (1.71-4.56)	<0.001
>80	8.52 (5.50-13.21)	<0.001	4.04 (2.49-6.57)	<0.001	5.60 (3.01-10.39)	<0.001	3.50 (1.81-6.80)	<0.001
Sex								
Female	Reference		Reference		Reference		Reference	
Male	1.46 (1.19-1.80)	<0.001	1.50 (1.21-1.85)	<0.001	1.40 (1.07-1.83)	0.014	1.40 (1.06-1.85)	0.017
Grade								
Well-differentiated	Reference		Reference		Reference		Reference	
Moderately differentiated	1.95 (1.44-2.64)	<0.001	1.41 (1.03-1.93)	0.033	2.65 (1.69-4.13)	<0.001	NA	0.128
Poorly differentiated	4.51 (3.25-6.26)	<0.001	1.51 (0.84-2.71)	0.169	7.14 (4.49-11.38)	<0.001	NA	0.532
Undifferentiated	10.62 (7.65-14.73)	<0.001	2.00 (1.09-3.68)	0.026	17.51 (11.04-27.78)	<0.001	NA	0.297
Unknown	15.53 (9.34-25.82)	<0.001	0.95 (0.49-1.85)	0.878	25.74 (12.37-53.56)	<0.001	NA	0.583
Histological type								
Chondrosarcoma, NOS	Reference		Reference		Reference		Reference	
Juxtacortical chondrosarcoma	0.51 (0.13-2.04)	0.340	0.71 (0.18-2.90)	0.636	0.86 (0.21-3.47)	0.830	1.10 (0.27-4.50)	0.900
Myxoid chondrosarcoma	1.61 (1.09-2.36)	0.016	1.19 (0.80-1.76)	0.400	2.02 (1.26-3.23)	0.003	1.72 (1.06-2.77)	0.027
Mesenchymal chondrosarcoma	3.61 (1.92-6.80)	<0.001	2.11 (1.03-4.33)	0.042	4.74 (2.22-10.14)	<0.001	2.37 (0.97-5.80)	0.058
Clear cell chondrosarcoma	1.45 (0.46-4.53)	0.523	1.72 (0.54-5.45)	0.360	NA	NA	NA	NA
Dedifferentiated chondrosarcoma	7.84 (6.21-9.92)	<0.001	3.00 (2.20-4.08)	<0.001	9.68 (7.14-13.13)	<0.001	3.43 (2.41-4.87)	<0.001
AJCC stage								
I	Reference		Reference		Reference		Reference	
II	3.90 (3.09-4.92)	<0.001	1.53 (0.89-2.61)	0.124	5.49 (4.00-7.54)	<0.001	2.91 (2.03-4.16)	<0.001
III	2.46 (1.09-5.55)	0.031	1.11 (0.35-3.53)	0.863	2.86 (0.90-9.08)	0.074	1.98 (0.42-9.34)	0.391
IV	14.12 (10.88-18.32)	<0.001	5.67 (3.64-8.82)	<0.001	24.47 (17.57-34.09)	<0.001	4.26 (1.69-10.79)	0.002
T-stage								
T1	Reference		Reference		Reference		Reference	
T2	3.13 (2.54-3.85)	<0.001	1.81 (1.46-2.25)	<0.001	3.82 (2.91-5.03)	<0.001	1.94 (1.44-2.60)	<0.001
T3	4.03 (2.29-7.11)	<0.001	2.20 (0.98-4.90)	0.055	4.40 (2.03-9.53)	<0.001	1.43 (0.50-4.10)	0.502

Table III. Continued.

	All-cause mortality				Cancer-specific mortality			
	Univariate Cox regression		Multivariate Cox regression		Univariate Cox regression		Multivariate Cox regression	
Characteristics	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
N-stage								
N0	Reference		Reference		Reference		Reference	
N1	3.95 (2.22-7.03)	<0.001	NA	0.167	5.19 (2.56-10.52)	<0.001	NA	0.260
M-stage								
M0	Reference		Reference		Reference		Reference	
M1	10.69 (8.33-13.71)	<0.001	NA	0.085	15.86 (11.79-21.34)	<0.001	3.13 (1.23-7.99)	0.017
Surgery								
No	Reference		Reference		Reference		Reference	
Yes	0.25 (0.19-0.32)	<0.001	0.39 (0.29-0.52)	<0.001	0.22 (0.16-0.30)	<0.001	0.54 (0.36-0.81)	0.003
Radiotherapy								
No	Reference		Reference		Reference		Reference	
Yes	2.16 (1.71-2.71)	<0.001	1.31 (1.03-1.67)	0.030	2.53 (1.89-3.39)	<0.001	1.47 (1.08-2.01)	0.015
Chemotherapy								
No	Reference		Reference		Reference		Reference	
Yes	4.44 (3.47-5.67)	<0.001	NA	0.943	6.19 (4.58-8.35)	<0.001	NA	0.827
Group								
Initial pCS	Reference		Reference		Reference		Reference	
Second pCS	1.87 (1.45-2.41)	<0.001	1.72 (1.31-2.26)	<0.001	1.18 (0.78-1.77)	0.429	NA	0.294

AJCC, American Joint Committee on Cancer; CI, confidence interval; NA, not applicable; pCS, primary chondrosarcoma; NOS, not otherwise specified.

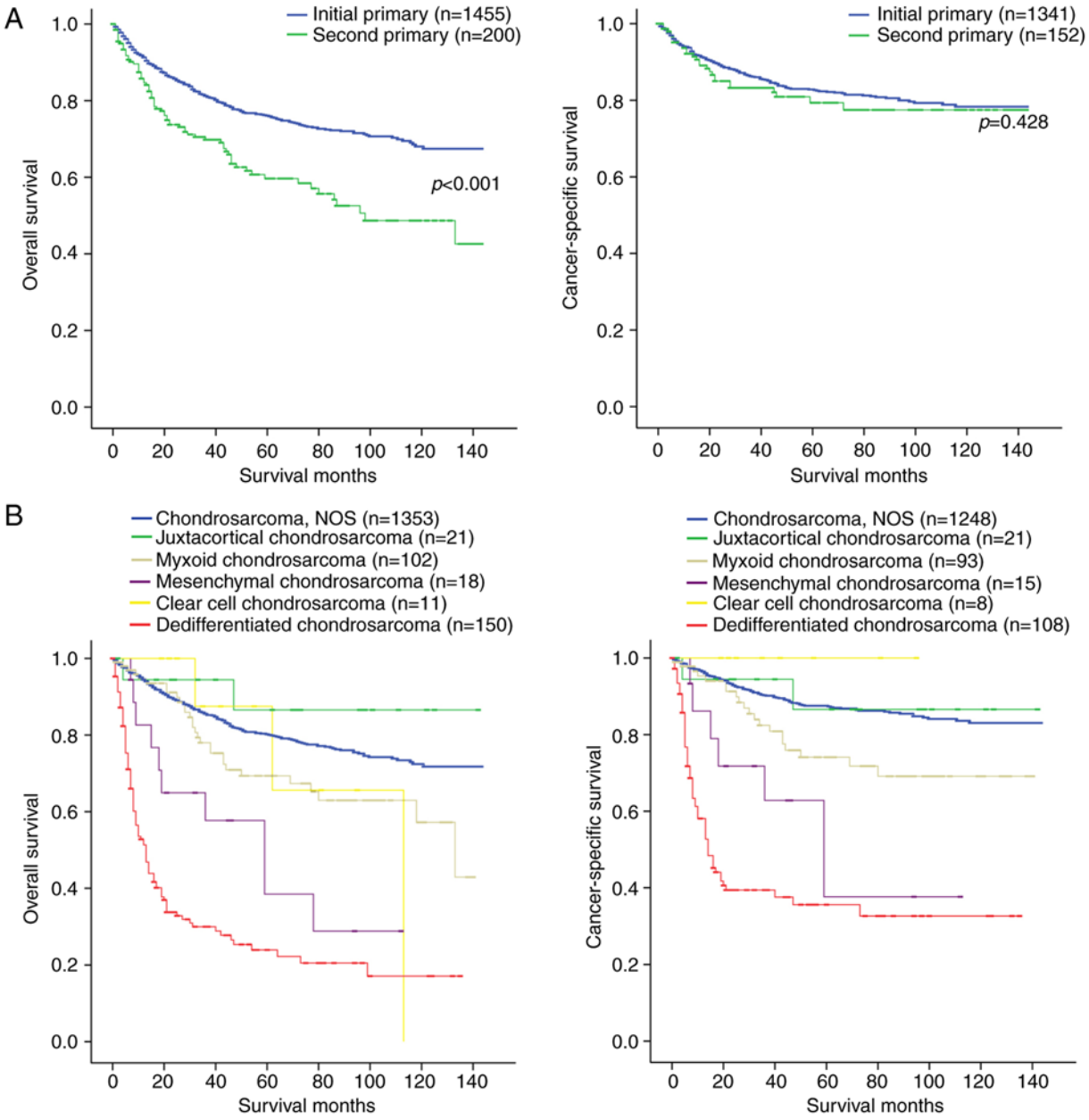

Figure 1. Kaplan-Meier analysis demonstrating the overall survival (left) and cancer-specific survival (right) of (A) patients with initial pCS and second pCS (log-rank tests, P<0.001) and (B) patients with different histological types. pCS, primary chondrosarcoma; NOS, not otherwise specified.

have focused on second primary tumours. By investigating 2,462 patients with hepatocellular carcinoma who underwent liver transplantation, Heo *et al* (24) revealed that patients with hepatocellular carcinoma who had received a liver transplantation had a longer life expectancy and higher risk of second primary cancer compared with the general population (standardized incidence ratios, 2.79; 95% CI, 2.27-3.38). Chen *et al* (25) demonstrated that the prognosis of patients with second primary colorectal cancer was worse than that of patients with initial primary colorectal cancer, and the therapeutic benefit on colorectal cancer prognosis was generally similar for the patients with initial and second primary colorectal cancer. The present study revealed similar results; it was identified that patients with second pCS had a worse prognosis compared with patients with initial pCS, and the treatment benefits were similar for patients with initial and second pCS. Surgery can significantly reduce all-cause mortality, while the use of radiotherapy or chemotherapy does not reduce all-cause mortality.

Furthermore, in terms of demographic and clinical characteristics, χ^2 tests revealed a significant difference in the age at diagnosis for patients with initial pCS and those patients with second pCS; patients with second pCS were diagnosed at an older age compared with patients with initial pCS.

The present study does have certain limitations. First, the research is based on the SEER database, a retrospective dataset that therefore has inherent limitations. Secondly, the patients' physical condition was unclear; patients with excessive comorbidities may pursue more conservative treatment. In addition, the number of patients included in the present study was small, so further prospective studies are necessary.

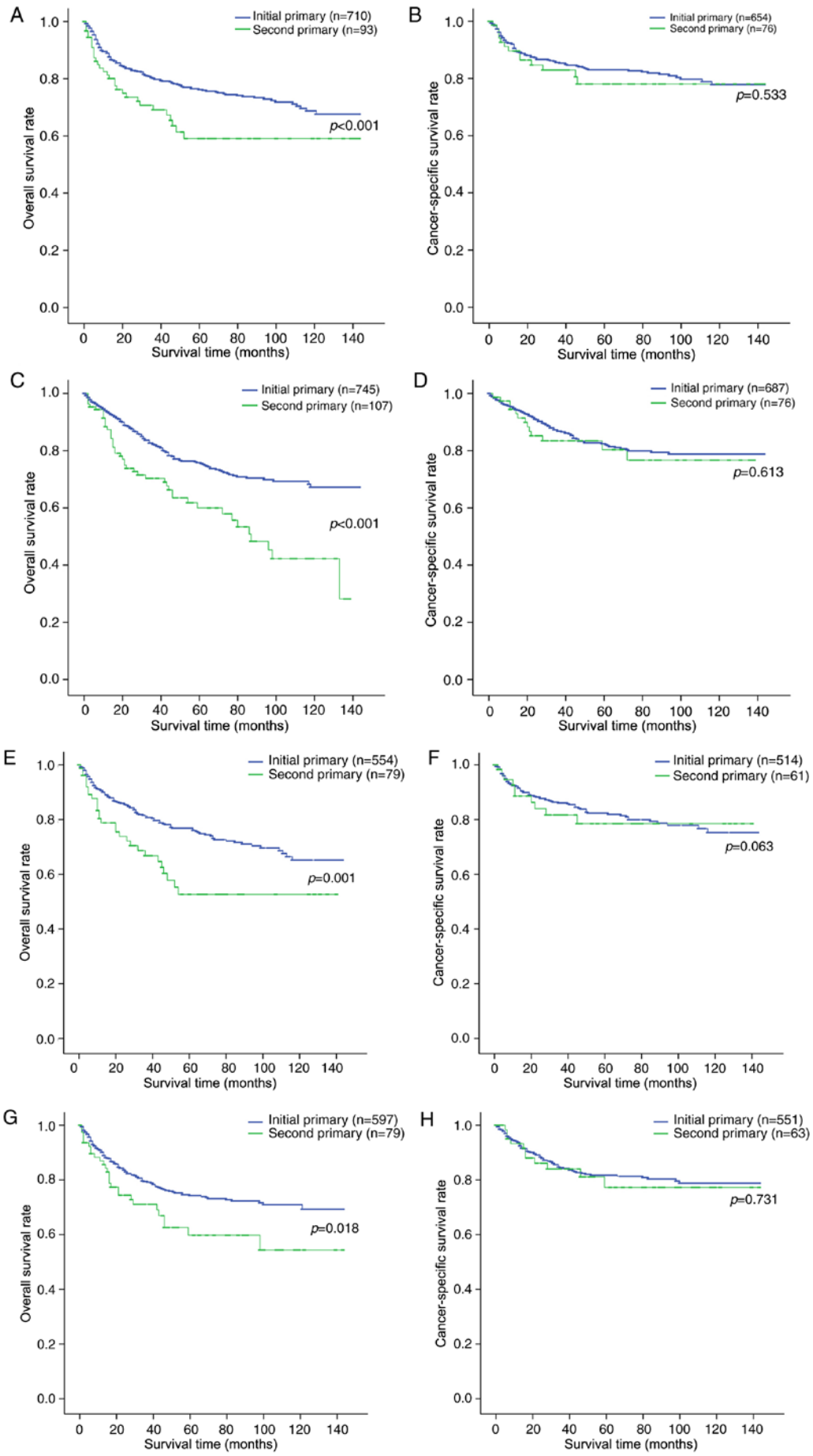

Figure 2. Overall survival (left) and cancer-specific survival (right) of patients with initial pCS vs. second pCS for (A and B) appendicular chondrosarcoma, (C and D) axial chondrosarcoma, (E and F) left-sided chondrosarcoma and (G and H) right-sided chondrosarcoma. pCS, primary chondrosarcoma.

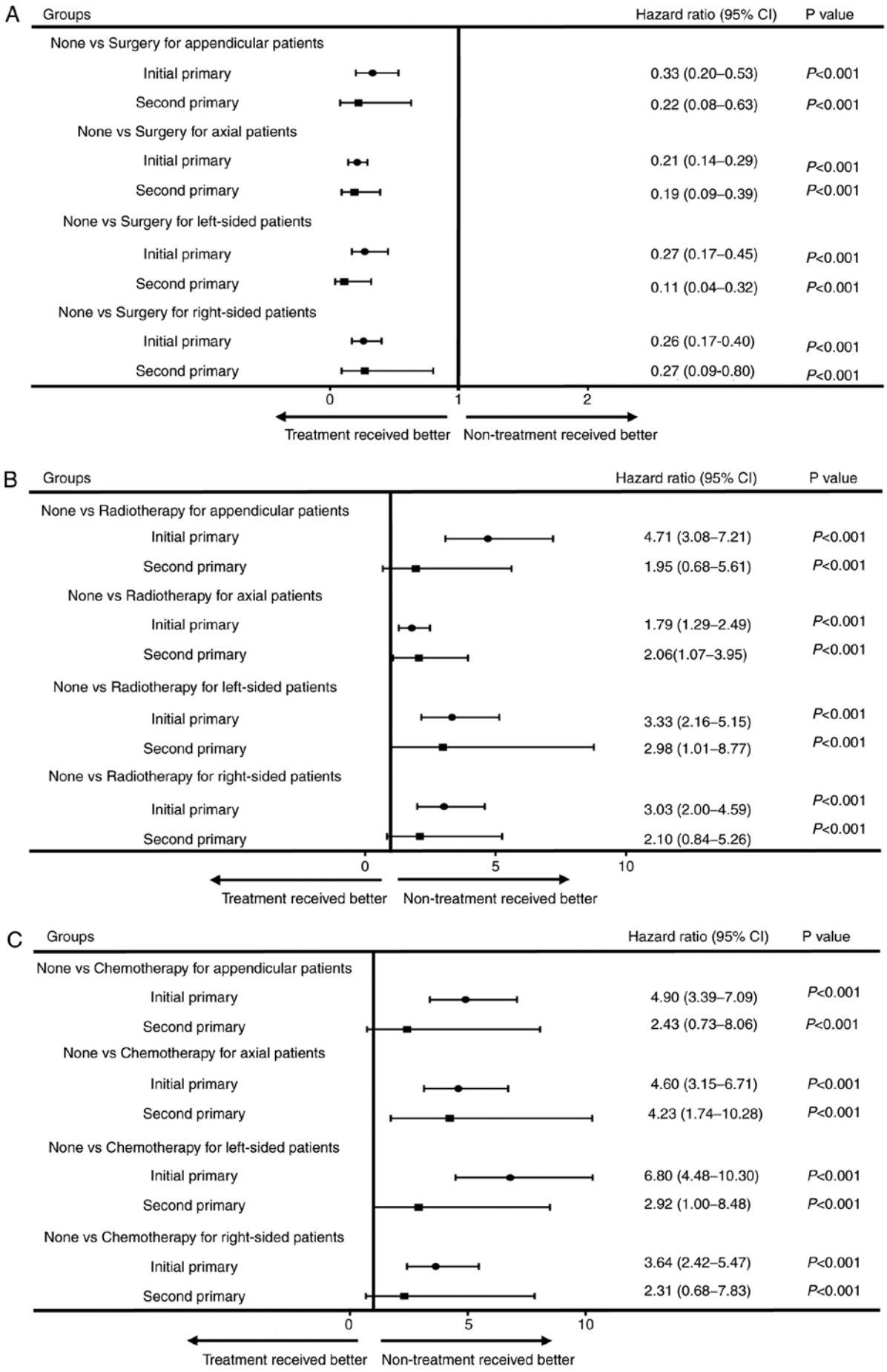

Figure 3. Forest plot presenting the interaction between patients with initial and second primary chondrosarcoma undergoing (A) surgical treatment, (B) radiotherapy and (C) chemotherapy. CI, confidence interval.

The results of the present study revealed that patients with second pCS were more frequently diagnosed at an older age and had a worse prognosis compared with patients with initial pCS. For patients with initial and second pCS, surgery was the main treatment method.

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Availability of data and materials

All the data generated or analyzed during the present study are included in this published article.

Authors' contributions

WM, JF and JG designed the research. HY and MK acquired the data. DW, XH and XY analyzed the results. WM wrote the article. JF and JG revised and provided critical comments. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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