Clinical statistical analysis with comparison between pelvic and non-pelvic chondrosarcoma

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Abstract

Background

Chondrosarcomas are a rare tumor that has a variable biological characteristic. Also, their treatment clinically and surgically is controversial. Analyze the clinical statistics and prognostic factors of pelvic chondrosarcoma to provide a reference for clinical diagnosis and treatment.

Method

A total of 73 cases of chondrosarcoma were collected, including 24 pelvic from 2008 to 2017 hospital database and divided into 2 groups of pelvic chondrosarcoma and non-pelvic chondrosarcoma. The clinical characteristics and prognostic factors of pelvic chondrosarcoma were analyzed by different statistic methods.

Result

Among the 24 pelvic chondrosarcoma patients, the ratio of male to female was 1.4:1, and the median age was 43.5 years. According to the classification proposed by Enneking, there were 5 in

area I, 14 in area II, and 5 in area III; Histological grading of chondrosarcoma grade I in 1 case, II in 15 cases, III in 8 cases; The histological type was 17 conventional, 3 dedifferentiated, 2 secondary, myxoid 1 and mesenchymal 1. The overall survival rates were 3, 5 and 10 years (82.2±8.1) %, (77.3±8.9) %, (52.4±12.1) % respectively. The local recurrence rate of pelvic chondrosarcoma after surgical resection (83.3%) was significantly higher than that of other sites (34.7%), and the difference was statistically significant (P=0.000); The final proportion of amputation rate (50.0%) was also higher than other parts (20.4%) with a statistically significant difference (P=0.000). But the total survival of the 2 groups is (P=0.216).

Conclusion

Chondrosarcoma of bone generally has an excellent prognosis when optimal diagnosed and treated by an experienced team of specialists. But pelvic chondrosarcoma has a higher local recurrence rate than the other sites and is tend to result in amputation. Early local recurrence after surgery indicates a poor prognosis.

Keywords pelvic chondrosarcoma; prognostic factors; tumor recurrence.

Introduction

Chondrosarcoma is a malignant tumor of cartilage origin, and its incidence rate is second in among primary malignant bone tumors [1]. It can be divided into different histological types according to histological characteristics and pathological sites. Besides, the tumors have considerable variation in outcome depending on size, histologic grade, Musculoskeletal Tumor Society (MSTS) stage, and tumor type. According to the incidence rate grading from a higher rate to lower rate follows: the common central type, conventional, dedifferentiated type, mesenchymal, myxoid type, clear cell type [1-2] are proposed. The tumor grade and the anatomic site are important because both influence the type of treatment and outcome. Chondrosarcoma responds poorly to traditional chemotherapy and radiotherapy. Whether responding to conventional adjuvant therapy for a higher-lower grade or advanced chondrosarcoma is still controversial [3-6]. Surgical treatment is the only known treatment with definite results at present. The pelvis is the second most common site of chondrosarcoma [7-8]. Due to the complicated and special anatomical structure, it's difficult for resection and reconstruction of the site, the intraoperative bleeding is high, and the incidence of surgical complications is high, so Its clinical treatment is always challenging[9]. In this study,

medical records of 24 patients with pelvic chondrosarcoma were retrospectively analyzed. Also, summarize the clinical statistics evidence of pelvic chondrosarcoma and analyze its prognostic factors.

Materials and methods

General information

A total of 78 cases of chondrosarcoma were confirmed by pathological examination and admitted to General Hospital from 2008 to 2017 according to the hospital medical record database. Five cases were not included in the study due to a lack of data. Out of the 73 included patients, 24 were pelvic chondrosarcomas; 14 males and 10 females with a ratio of 1.4:1. The patients were aged from 22 to 69 years, with a median age of 43.5 years. Pelvic tumors were partitioned according to the Enneking system [10], located 5 cases in area I, 14 cases in area II, 5 cases in area III. All patients were accepted puncture or incision biopsy. Histological grading of chondrosarcoma I grade 1 case, II grade 15 cases, 8 cases in III grade; The histological type was normal central type in 17 cases, dedifferentiated type in 3 cases, secondary type in 2 cases, myxoid type and mesenchymal type each 1 case. To better understanding all subtype of chondrosarcoma, the author collected all data and summarized in **Table 1.**

Table 1- Overview of clinical characteristics and therapeutic options in all subtypes of chondrosarcoma of bone:

	Conventional primary central chondrosarcoma	**Conventional secondary peripheral chondrosarcoma**	**Dedifferentiated chondrosarcoma**	**Mesenchymal chondrosarcoma**	**Clear cell chondrosarcoma**
% of all chondrosarcoma	~75%	~10%	~10%	<2%	<2%
Precursor lesion	Enchondroma (up to 40%?)	Osteochondroma (100%)	Conventional chondrosarcoma	None	None
Occurrence within syndrome	Enchondromatosis (Ollier disease)	Multiple osteochondromas (MOs)	Rarely in MOs or enchondromatosis	None	None
Age	>50 years	Younger than central chondrosarcoma	Median age 59 years	Any age (peak in second and third decade)	Any age (peak in third to fifth decade)
Preferential location	Pelvis, proximal femur, proximal humerus, distal femur, ribs	Pelvis, shoulder girdle bones	Femur and pelvis	65%–86% skeleton (jawbones, ribs, ilium, vertebrae) 14%–43% Extra-osseous (meninges)	Epiphysis of humeral or femoral head
Histological grading	Grade I–III	High grade	High grade	Low grade	
Survival	Grade I, 83%; grade II, 64%; grade III, 29% at	24% at 5 years	28% at 10 years	89% at 10 years	

	10 years				
Sensitivity to chemotherapy	None	None	Uncertain	Possibly, if high percentage round cells	None
Sensitivity to radiotherapy	Low	Low	Low		Low
Potential targets for therapy	PTHLH (BCL2), IHH, PDGFR-a, COX-2, MMP, ER, HDAC	PTHLH (BCL2), ER, HDAC	None	BCL2, c-PKC-a, PDGFR-a	PTHLH (BCL2), PDGF, MMP2, IHH

* Abbreviations: BCL2=*B-cell lymphoma 2 protein*; COX-2=*cyclooxygenase 2*; ER=*estrogen receptor*; HDAC=*histone deacetylase*; IHH=*Indian hedgehog*; MMP=*matrix metalloproteinase*; PDGFR-*a=platelet-derived growth factor receptor a*; PTHLH=*parathyroid hormone-like hormone*.

Treatment

All 24 cases of pelvic chondrosarcoma underwent surgical treatment, including 15 cases of resection and reconstruction in the first operation, 8 cases of resection and no reconstruction, and 1 case of hip amputation (when the patient was found, the tumor was huge and invaded major blood vessels and important nerves, so limb salvage operation was not possible). 16 patients underwent 2 or more operations due to local recurrence or postoperative dysfunction, of which 12 were ended up with amputations. A total of 5 patients were treated with chemotherapy, including 1 preoperative chemotherapy and 4 postoperative chemotherapy. The chemotherapy regimen includes ifosfamide + doxorubicin + azolidazole, ifosfamide + doxorubicin, or methotrexate + epirubicin. 3 patients were treated with postoperative radiotherapy.

Follow-up

The patient should be followed up to the clinic once every 3 months for the re-examination of the surgical site's X-ray and chest radiographs within 2 years of the surgery. Computed tomography (CT) or magnetic resonance imaging (MRI) should be performed if required. If there were no signs of progress, the follow-up was changed to once every six months after 2 years and once every year after 5 years. Follow-up records included local recurrence and distant metastasis. If the patient died, the time of death was confirmed by telephone follow-up. The duration of follow-up was defined as from the time of diagnosis until the patient died or was counted.

Statistical analysis

IBM SPSS Statistics 24.0 software was used for data collection and statistical analysis. Pearson $\chi 2$ test was used to test the correlation between the two categorical variables, and Fisher's exact

probability method was used if the frequency was <5. Kaplan-Meier method was used to analyze survival and estimate survival rate. COX regression model was used for univariate analysis of survival time. When these variables are incorporated into the COX regression model for multi-factor analysis, the independent variables are screened by the advanced method based on maximum likelihood estimation. P<0.05 indicated that the difference was statistically significant.

Results

Clinical features of pelvic chondrosarcoma

Chondrosarcomas of the pelvis were rarely classified as grade I, with only 1 in 24 (3.8%), compared to 26.5% in other chondrosarcomas. The local recurrence rate of pelvic chondrosarcoma was significantly higher than the other sites 83.3% (20 cases), but only 34.7% (17 cases). During treatment, the percentage of lesions located in the pelvis that eventually underwent amputation was significantly higher than in non-pelvic areas (50.0% in 12 cases). 3 patients (12.5%) with pelvic chondrosarcoma received postoperative radiotherapy, but no patients with tumors of other sites receiving radiotherapy. A total of 73 patients with chondrosarcoma were included in this study with a male to female ratio of 1.03:1, showing no significant gender bias. There was no statistically significant difference in the gender, age, chemotherapy or distant metastasis between pelvic chondrosarcoma patients and non-pelvic chondrosarcoma patients. (**Table 2, Figure 1**)

Table 2- Different characteristics between pelvic and non-pelvic chondrosarcomas:

Factors	Pelvis/n(%)	Other parts/n(%)	χ2 value	P-value
Gender			0.837	0.360
Female	10 (41.7)	26 (53.1)		
Male	14 (58.3)	23 (46.9)		
Age			0.89	0.345
< 50 years	16 (66.7)	27 (55.1)		
> 50 years	8 (33.3)	22 (44.9)		
Histological grade			5.307	0.070
I grade	1(4.2)	13 (26.5)		
II grade	15 (62.5)	22 (44.9)		
III grade	8 (33.3)	14 (28.6)		
Amputation			6.7	0.010
Yes	12 (50.0)	10 (20.4)		
Not	12 (50.0)	39 (79.6)		
Chemotherapy			-	0.720 ①
Yes	4(16.7)	6(12.2)		

Not	20 (83.3)	43 (87.8)		
Radiotherapy			-	0.033 ①
Yes	3 (12.5)	0 (0.0)		
Not	21 (87.5)	49 (100.0)		
Local recurrence			-	0.000 ①
Yes	20 (83.3)	17 (34.7)		
Not	4(16.7)	32 (65.3)		
Metastasis			0.991	0.319
Yes	8 (33.3)	11 (22.4)		
Not	16 (66.7)	38 (77.6)		

Note: ①=Fisher's exact test.

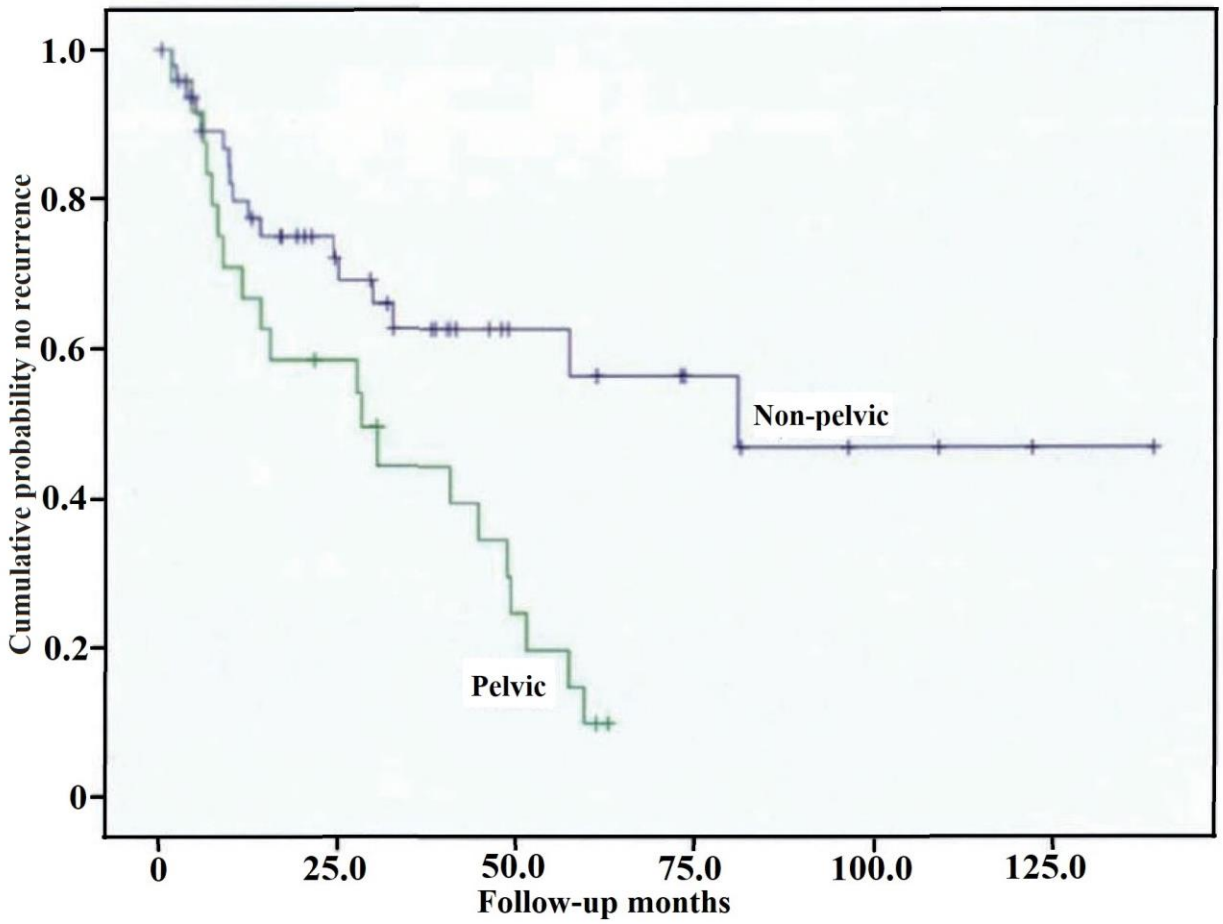

Figure 1

Recurrence and metastasis of pelvic chondrosarcoma

Diagnostic methods for local recurrence or distant metastasis include CT, MRI, isotope bone scan, PET-CT, and biopsy. In this study, the I area of patients is 5 cases, 2 underwent reconstruction with allograft bone graft, and all postoperatively recovered well; area II hip joint tumor and if do surgery then generally need to rebuild with restoring joint function. In this study, 9 of the 14 patients were constructed with artificial weight (saddle prosthesis or artificial acetabular cup), among 3 had a deep infection, and 2 had dislocation; There were no complications in 1 case of artificial bone grafting and 1 case of pelvic amputation. Only 3 cases were cleared without reconstruction, 1 of which was complicated with deep postoperative infection. The pelvic chondrosarcomas surgically removed, and at least 1 local recurrence occurred in 20 patients. Recurrence interval refers to the time from surgery to local recurrence (if any), ranging from 1.7 to 59.4 months, with a median time of 21.7 months. The survival of patients with pelvic chondrosarcoma without local recurrence was shorter than patients with other tumors (P=0.005). The time interval between surgery and distant metastasis was 5.2 - 66.0 months, and the median time was 32.4 months. The distant metastases included 5 cases of lung, 1 case of the abdominal cavity, 1 case of retroperitoneum, and 1 case of multiple metastases of lung and abdominal cavity. In comparison, patients with high differentiation in other parts accounted for 26.5%, indicating that chondrosarcoma of the pelvis was more malignant. In this study, pelvic chondrosarcoma was the second most common site of the disease after the femur accounting for 32.9%, which is slightly higher than similar studies [7,12].

Prognostic analysis of pelvic chondrosarcoma

The median follow-up time of 73 patients with chondrosarcoma was 60.1 months, with 21 deaths, 50 cases surviving, and 4 cases missing in the follow-up. The overall survival rates at 3, 5 and 10 years were (86.9±4.1) %, (79.5±5.2) %, and (64.7±6.9) % respectively. The median follow-up time of 24 patients with pelvic chondrosarcoma was 67.4 months including 13 patients died, 11 surviving, and 2 missing in the follow-up. The 3, 5 and 10-year survival rates were (82.2±8.1) %, (77.3±8.9) %, and (52.4±12.1) % respectively.

The total survival time of pelvic and non-pelvic chondrosarcoma patients was not significantly different (P=0.216), as shown in **Figure 2.** The univariate analysis shows the overall survival time of patients with pelvic chondrosarcoma, including variables such as gender, age at diagnosis at <50 years, tumor's Enneking grade system, maximum diameter > 8 cm, histological grade, final

amputation, chemotherapy & radiotherapy whether or not, recurrence or not, and whether the time from surgery to recurrence within <1 year. The results showed a significantly shorter survival time for patients with local recurrence within 1 year (P = 0.001), as shown in **Figure 3**. Further multivariate analysis indicated that local recurrence was the only independent prognostic factor within 1 year. Patients' gender, age, tumor site, size, histological grade, eventual amputation, chemotherapy or radiotherapy, and recurrence were not related to overall survival (**Table 3**).

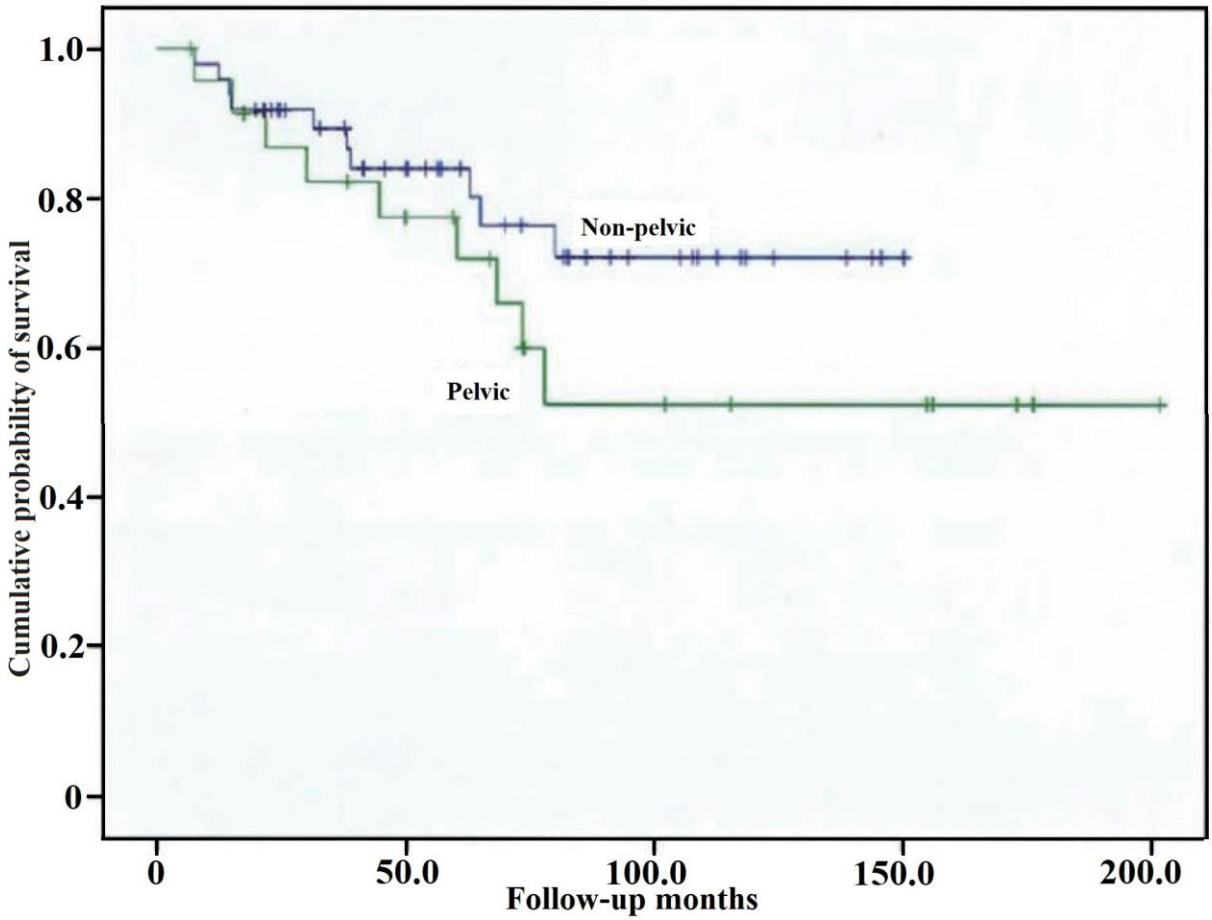

Figure 2

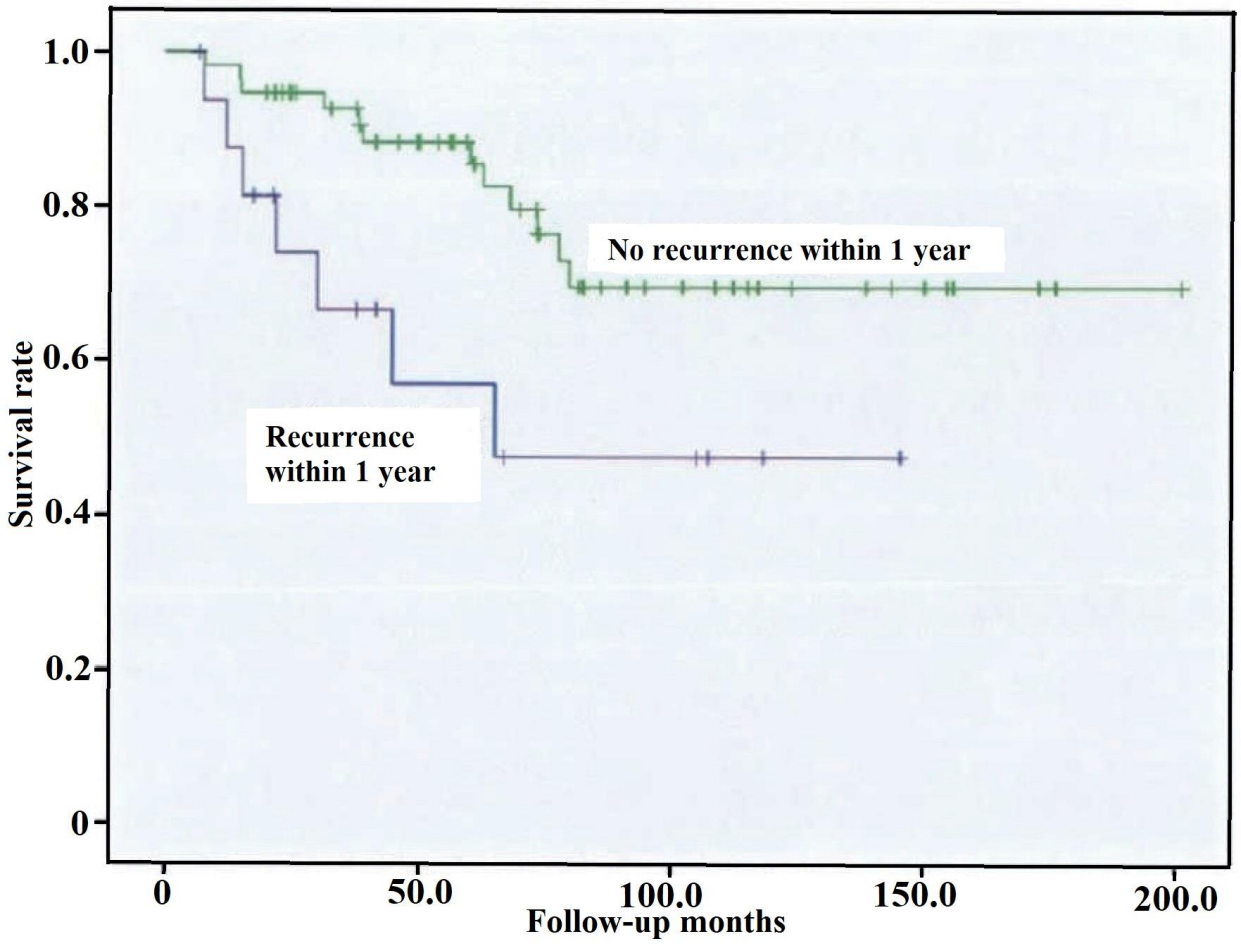

Figure 3

Table 3- Univariate prognostic factors analysis of pelvic chondrosarcomas:

Factors	n	HR	95% Cl	P-value
Gender				0.780
Female	10	1.185	0.360 ~ 3.899	
Male	14	-		
Age				0.130
< 50y ears	16	0.394	0.118 ~ 1.317	
> 50 years	8	-		
Enneking system				0.379
I area	5	1.944	0.353 ~ 10.694	
II area	14	0.767	0.148 ~ 3.972	
III area	5	-		
Maximum diameter of tumor				0.280
< 8 cm	10	1.926	0.586 ~ 6.327	

> 8 cm	14	-		
Pathological grade				0.759
I grade	1	0	>0.000	
II grade	15	0.637	0.194 ~ 2.093	
III grade	8	-		
Amputation				0.963
Yes	12	0.963	0.287 ~ 3.288	
Not	12	-		
Chemotherapy				0.297
Yes	5	1.925	0.562 ~ 6.594	
Not	19	-		
Radiotherapy				0.764
Yes	3	1.267	0.271 ~ 5.920	
Not	21	-		
Local recurrence				0.303
yes	20	28.761	0.048 ~ 17.239	
Not	4	-		
Time between surgery & recurrence				0.001
< 1 years	8	17.032	3.197 ~ 90.745	
> 1 years	16	-		

Discussion

The pelvic anatomical structure is complicated. Pelvic tumor surgery is difficult with high risk and many postoperative complications. This study analyzes and summarizes the clinical statistics and prognostic factors of pelvic and non-pelvic chondrosarcoma to provide a reference for the clinical diagnosis, treatment of the disease, and to improve the patient's life quality. The age range was 17 to 87 years, with a median age of 46 years, showing demographic characteristics similar to those of previous studies [7, 11-12]. Pelvic tumors were partitioned according to Enneking [10], and the largest proportion of tumors were in area II, reaching 58.3%; because they involve the hip joint, and it is undoubtedly increasing the difficulty of surgery. The size of the tumor varied depending on whether the tumor was located in the pelvis. The mean maximum diameter of the tumor in the pelvis was 10.5 cm, while that in other parts was 7.1 cm. There were also significant differences in tumor grades according to different sites. The histological manifestations of chondrosarcoma of the pelvis were very few (4.2%), and most of them were of medium and low differentiation.

Pelvic chondrosarcoma is not easy to be diagnosed and treated early. The main reason is that there is a large space in the pelvis for tumor growth, resulting in obvious swelling, compression, pain,

and other symptoms later. Chondrosarcoma should be highly suspected in cases of pelvic tumors, where a puncture or open biopsy indicates the origin of cartilage carefully identify. If it is confirmed as a benign tumor, then it should be followed up closely postoperatively and alert to secondary malignant changes. In this study, 2 cases (8.3%) were secondary chondrosarcomas of benign tumors. Surgical procedures for pelvic chondrosarcoma may be selected according to the Enneking subdivision. Attention should be paid to the operation because the sciatic nerve out of the outside of the pelvis often and has iliac vessels branch of the superior gluteal blood vessels through.

The surgeon mustn't avoid the first ligation of the blood vessels to avoid the occurrence of uncontrolled bleeding.

Adequate soft tissue coverage is the key to the success of the operation. Compared with traditional customized prosthesis 3D printing can achieve a satisfactory reconstruction effect; This kind of prosthesis has been routinely used in our hospital in recent years because of its good Angle matching in the acetabular cup and the difficulty of femoral head dislocation. If the tumor in area III does not involve the hip joint, only sitting and pubic resection will have less damage to the stability of the pelvis and do not affect the function of the hip joint. It can only be filled with a bone graft or rebuild. Since the sciatic tubercle is closer to the sciatic nerve, the sciatic nerve should be fully exposed and protected during surgery to avoid injury. In this study, 2 of the 5 patients underwent artificial hip reconstruction due to the involvement of the hip joint, of which 1 had deep postoperative infections; 2 had the only resection and 1 had no significant complications after amputation. Area IV is the metatarsal tumor, if total metatarsal resection is performed, reconstruction is required; Generally, a screw rod system is used to connect the spine and the metatarsal bone to maintain the stability of the pelvic ring [13]. This study did not include this type of case.

Non-surgical treatments for chondrosarcomas are limited and the efficacy of chemotherapy for chondrosarcoma remains controversial [3-5]. However, Kawaguchi et al. [6] showed that for dedifferentiated chondrosarcomas, surgical resection combined with ifosfamide chemotherapy resulted in significantly longer disease-free survival than patients treated with surgery alone. Italiano et al. [14] studied the response of advanced chondrosarcomas to chemotherapy (unretractable or with distant metastasis), showing that multi-drug combination chemotherapy can significantly delay the onset of disease progression, especially in patients with mesenchymal and

dedifferentiated chondrosarcomas. Some scholars have also explored targeted therapy for chondrosarcoma, focusing more on chemokine receptor 4 (CXCR4). This receptor can increase the expression of vascular endothelial growth factor (VEGF), induce angiogenesis and improve cell invasiveness [15]. Sun et al. [16] have successfully inhibited tumor growth and lung metastasis in a mouse chondrosarcoma transplantation model with its specific blocking drug AMD3100**.** Therefore, for mesenchymal and dedifferentiated chondrosarcomas, adjuvant chemotherapy can be used to control the progression of the disease if the tumor is characterized by rapid growth, blurred boundary, multiple postoperative recurrences and other features indicating a high degree of malignancy. Further research is needed to find more sensitive drugs to standardize adjuvant therapy. It is generally believed that chondrosarcoma is not sensitive to radiotherapy, and possible reasons include the deletion of tumor suppressor gene P16 in chondrosarcoma cells and increased expression of anti-apoptotic proteins such as Bcl-2, Bcl-xL and XIAP [17]. Previous clinical studies also mostly confirmed that radiotherapy could not improve the prognosis of chondrosarcoma [18-19]. However, a retrospective study of 31 cases of pelvic chondrosarcoma by Outani et al. [20] showed that carbon ion radiotherapy had no significant effect on the survival time of patients, and the limb function of the patients was significantly better than the surgery group.

A clinical trial by Uhl et al. [21] also showed that carbon-ion radiotherapy for middle and low-level cranial base chondrosarcoma could achieve better local control with fewer adverse reactions. carbocation radiotherapy is a trial-and-true treatment option for pelvic chondrosarcoma patients who are difficult to treat surgically and not sensitive to chemotherapy. In this study, 3 patients with pelvic chondrosarcoma were treated with radiotherapy, 2 of whom were treated with radiotherapy after amputation and had died at the time of follow-up. In this study, pelvic chondrosarcoma was more likely to recurrence with a local recurrence rate of 83.3% after surgical resection. Combined with the existing studies, it can be found that the local recurrence rate after resection varies greatly with different sites and operation methods. Roos et al. [22] reported a local recurrence rate of 17.1% within 5 years after primary rib chondrosarcoma resection. Al-Refaie et al. [23] reported a local recurrence rate of 4.4% after chest wall chondrosarcoma. Yin et al. [18] reported the local recurrence rate of chondrosarcoma after the operation was 42.9%. Ogose et al. [24] reported that the postoperative recurrence rate of hand and foot chondrosarcoma was 40.4%, and the recurrence rate was closely related to the surgical procedure. Tumor recurrence after amputation, lesion

resection and curettage the rates decreased in turn, which suggests that sufficient resection range can reduce the local recurrence rate.

In this study, it was found that recurrence did not affect the overall survival time of patients, but the prognosis of patients with earlier recurrence (<1 year) was poor, which was consistent with the existing research results [19]; which may be a manifestation of the high malignant degree of the tumor. In this study, the proportion of pelvic chondrosarcoma with metastasis was 33.3% and the sites were lung, abdominal cavity and retroperitoneal. Previous studies have also shown that chondrosarcomas are most likely to metastasize to the lungs [18, 25-26]. Compared with other chondrosarcomas, the proportion of spinal metastasis was 24.5% [18], 17.1% [24], and 11.8% [22]. The probability of pelvic metastasis is relatively high, which is consistent with previous research results suggesting that the overall malignant degree of pelvic chondrosarcoma is higher than other sites [8]. This study has some limitations and it may also have susceptible to bias associated with certain patients being reported over others, so further study should be conducted.

Conclusion

The local recurrence rate after surgical resection of pelvic chondrosarcoma was significantly higher than other chondrosarcomas, and the final amputation rate was also significantly higher. Local recurrence within 1 year after surgery is an independent prognostic factor for pelvic chondrosarcoma. Some findings of this study are supported previously published literatures. Analysis of the difference between surgical techniques, clinical statistics, prognostic factors, and patient outcomes has been limited because of the rarity of these lesions and few institutions having enough patients to study about it.

Abbreviation

None

Ethical approval

The ethics committee approved this manuscript and design plan.

Statement of Informed Consent

No consent was needed because the database is publicly available and does not include unique patient identifiers.

Availability of data and materials

By reasonable request, the author will provide data.

Authors' contributions

SAJ & SJ conceived and designed the study; SAJ, BSR, LCH, and ZZ collected the data; SAJ, BSR & LCH checkout the follow-up; SAJ, ZZ & BSR wrote different parts of the manuscript; SJ revised the manuscript.

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Interests of competing

None of the authors have competing interests**.**

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