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Prognostic Factors in Dedifferentiated Chondrosarcoma: A Retrospective Analysis of a Large Series Treated at a Single Institution

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Background. Dedifferentiated chondrosarcomas (DDCSs) are highly malignant tumors with a dismal prognosis and present a significant challenge in clinical management. Methods. In an IRB approved retrospective protocol, we identified 72 patients with DDCS treated at our institution between 1993 and 2017 and reviewed clinicopathological characteristics, treatment modalities, and outcomes to analyze prognostic factors. Results. Femur (44.4%), pelvis (22.2%), and humerus (12.5%) were most commonly involved sites. Twenty-three patients (31.9%) presented with distant metastasis, and 3 (4.2%) of them also had regional lymph node involvement. The median overall survival (OS) was 13.9 months. On multivariate analysis, pathological fracture, larger tumor size, lymph node involvement, metastasis at diagnosis, extraosseous extension, and undifferentiated pleomorphic sarcoma component correlated with worse OS, whereas surgical resection and chemotherapy were associated with improved OS. For progression-free survival (PFS), pathological fracture and metastasis at diagnosis showed increased risk, while chemotherapy was associated with decreased risk. Among patients who received chemotherapy, doxorubicin and cisplatin were significantly associated with improved PFS but not OS. Among patients without metastasis at diagnosis, 17 (34.7%) developed local recurrence. Thirty-one (63.3%) developed distant metastases at a median interval of 18.1 months. On multivariate analysis, R1/R2 resection was related with local recurrence, while macroscopic dedifferentiated component was associated with distant metastasis. Conclusions. The prognosis of DDCS is poor. Complete resection remains a significant prognostic factor for local control. Chemotherapy with doxorubicin and cisplatin seems to have better PFS. More prognostic, multicenter trials are warranted to further explore the effectiveness of chemotherapy in selected DDCS patients.

1. Introduction

Dedifferentiated chondrosarcoma (DDCS) is a type of cartilaginous tumor that is comprised of two distinct components: (1) low-grade chondrogenic components and (2) high-grade noncartilaginous sarcoma. It constitutes 1-2% of all primary bone tumors [1]. Approximately 7–20% of low-grade chondrosarcomas can be expected to dedifferentiate [1–5]. DDCS is slightly more frequent in males. Patients with DDCS are older than those with conventional lesions, with a mean age of around 60 years (range: 15–90 years) [1, 3, 6–9]. The most common sites
were the femur and pelvis, followed by humerus and scapula [1, 3, 6].

It has been postulated that the dedifferentiated and cartilaginous components arise from a common primitive mesenchymal progenitor cell with the ability to express features of more than one line of mesenchymal differentiation [10]. However, the separation of the two clones is considered a relatively early event in the tumorigenesis of DDCS and further alterations may lead to the “switch” to a high-grade dedifferentiated chondrosarcoma [11–14]. Histological features of the anaplastic, noncartilaginous component are usually undifferentiated pleomorphic sarcoma (UPS); however, other types of sarcomas include osteosarcomas, fibrosarcomas, angiosarcomas, rhabdomyosarcomas, or leiomyosarcomas [1, 15]. UPS dedifferentiation was reported to be related with poorer outcomes [3]; however, other studies did not reveal any difference in the clinical outcome with different types of the dedifferentiated component [6, 16].

The prognosis of DDCS is dismal. Distant metastasis, especially to the lungs, is common both at the initial presentation and during or relatively soon after initial treatment [6, 17, 18]. The 5-year survival rate can be as low as 7%–24%, with median survival ranging from 5 to 13 months [3, 6, 7, 18–20]. Because of the rarity of DDCS and the insufficient number of large-scale studies, current reports regarding the potential prognostic factors are still inconclusive. One population-based study using the Surveillance, Epidemiology, and End Results (SEER) database suggested that chest wall location predicted better prognosis, whereas larger tumor size, presence of metastases at diagnosis, and no surgical resection were significant predictors of mortality [7]. Another study which utilized the network of member centers of the European Musculo-Skeletal Oncology Society (EMSOS) indicated that pathological fracture, pelvic location, and increasing age predicted poor survival and inadequate excision margins were related to local recurrence and mortality [6]. In addition, there is a lack of convincing evidence on the effectiveness of chemotherapy [1, 3, 6, 18, 20].

In this study, we aim to characterize the impact of clinicopathological features and treatment modalities on the clinical outcomes of patients with DDCS treated at our institution and to investigate prognostic factors.

2. Materials and Methods

2.1. Patient Selection. Our IRB approved institutional sarcoma database includes 13,412 patients from the 1960s to 2017. Study data were collected and managed using Research Electronic Data Capture (REDCap) electronic data capture tools [21]. The database retrospectively collects data from our institution’s clinical records, on patient demographics, primary and secondary tumor characteristics, treatment, follow up, and survival data. We queried the database for patients who were diagnosed with DDCS that was confirmed by pathology review at our institution by expert sarcoma pathologists and were treated in our institution between 1993 and 2017.

A total number of 72 patients were identified. Patient demographics and treatment characteristics are summarized in Table 1. Tumor sites are shown in Figure 1. There were 45 men and 27 women with a median age of 60.5 years (range: 29–92 years). Two patients had Ollier’s disease, and one had hereditary multiple exostoses. Seventeen patients had a known history of enchondroma (n = 5), low-grade chondrosarcoma (n = 5), or a bone lesion without further biopsy (n = 7) for over 1 year, with the longest present for 15 years. The size of the tumor at the time of diagnosis was available in 66 patients, which averaged 12.4 cm (median: 10.4 cm, range: 3.0–46.0 cm). Twenty-three patients (31.9%) presented with distant metastasis at the time of diagnosis, including lungs (n = 20, 27.8%), bones (pelvic bone, rib, skull, and spine, n = 5, 6.9%), soft tissue (buttock, chest wall, groin, and thigh, n = 4, 5.6%), liver (n = 1, 1.4%), and heart (n = 1, 1.4%), and 3 (4.2%) of them also had regional lymph node involvement.

2.2. Treatment Modalities. Of the 49 patients who did not have identifiable metastases at the initial presentation (M0), 48 received tumor excision (alone in 32, preoperative radiation therapy (RT) in 6, postoperative RT in 6, and both pre- and postoperative RT in 4) and one had RT alone for the primary tumor. Chemotherapy was administered preoperatively alone in 3 patients, postoperatively alone in 7 patients, both preoperatively and postoperatively in 3 patients, and prior to RT in 1 patient. Regimens used include ifosfamide alone (n = 1) and combinations of doxorubicin and cisplatin (AP) alone (n = 2) or with ifosfamide (n = 1)/ifosfamide and etoposide (IE, n = 1), methotrexate with AP (MAP, n = 5), methotrexate with IE (n = 1), IE alone (n = 1), and doxorubicin and ifosfamide (AI, n = 1) (1 regimen unknown). One patient who was treated with MAP also received the regimen of doxorubicin, ifosfamide and dacarbazine. Of the 6 patients who received neoadjuvant chemotherapy, one had 80% tumor necrosis after MAP, one had 70% necrosis following AP, and another two both had 30% necrosis after the treatment of MAP or methotrexate with IE.

Of the 23 patients who presented with metastasis (M1), 21 underwent surgical excision of the tumor and/or RT to the primary tumor (15 surgery alone, 2 surgery then postoperative RT, 1 surgery with pre- and postoperative RT, and 3 RT alone). Chemotherapy was given to 11 patients, among whom, 2 received preoperative chemotherapy with MAP or methotrexate alone, 6 had postoperative chemotherapy with doxorubicin alone (n = 1), AP (n = 1), or MAP alone (n = 1) or with ifosfamide (n = 1)/IE (n = 1) (1 regimen unknown), 1 had preoperative methotrexate and cisplatin and postoperative ifosfamide, 1 received AI after RT, and 1 had palliative chemotherapy alone (regimen unknown). Only two of these patients had an assessment of chemotherapy response following neoadjuvant chemotherapy and surgical excision, and the necrosis was 5% with MAP and 70% after methotrexate and cisplatin, respectively.

2.3. Statistical Analysis. Statistical significance between groups was analyzed using the chi-squared test or Fisher's
Table 1: The clinicopathological characteristics and treatment modalities in patients with dedifferentiated chondrosarcoma.

| Characteristics                       | Total | Nonmetastatic | Metastatic |
|---------------------------------------|-------|---------------|------------|
| **Age**                               |       |               |            |
| ≤60 years                             | 34 (47.2%) | 25 (51.0%) | 9 (39.1%) |
| >60 years                             | 38 (52.8%) | 24 (49.0%) | 14 (60.9%) |
| **Gender**                            |       |               |            |
| Female                                | 27 (37.5%) | 18 (36.7%) | 9 (39.1%) |
| Male                                  | 45 (62.5%) | 31 (63.3%) | 14 (60.9%) |
| **Pathological fracture**             |       |               |            |
| Yes                                   | 28 (38.9%) | 16 (32.7%) | 12 (52.2%) |
| **Site**                              |       |               |            |
| Extremity                             | 47 (65.3%) | 30 (61.2%) | 17 (73.9%) |
| Trunk                                 | 25 (34.7%) | 19 (38.8%) | 6 (26.1%) |
| **Tumor size**                        |       |               |            |
| ≤8 cm                                 | 20 (27.8%) | 14 (28.6%) | 6 (26.1%) |
| >8 cm                                 | 48 (66.7%) | 31 (63.3%) | 17 (73.9%) |
| Discontinuous                         | 4 (5.6%) | 4 (8.2%) | 0 (0.0%) |
| **Lymph node involvement**            |       |               |            |
| No                                    | 3 (4.2%) | 0 (0.0%) | 3 (13.0%) |
| Yes                                   | 9 (12.5%) | 5 (10.2%) | 4 (17.4%) |
| NA                                    | 17 (23.6%) | 9 (18.4%) | 8 (34.8%) |
| **AJCC 7th edition stage**            |       |               |            |
| II                                    | 45 (62.5%) | 45 (91.8%) | 0 (0.0%) |
| III                                   | 5 (6.6%) | 4 (8.2%) | 0 (0.0%) |
| IV                                    | 23 (31.9%) | 0 (0.0%) | 23 (100.0%) |
| **Extra-osseous extension**           |       |               |            |
| No                                    | 69 (95.8%) | 46 (93.9%) | 23 (100.0%) |
| Yes                                   |          |               |            |
| NA                                    |          |               |            |
| **Lymphovascular invasion**           |       |               |            |
| No                                    | 46 (63.9%) | 35 (71.4%) | 11 (47.8%) |
| Yes                                   | 9 (12.5%) | 5 (10.2%) | 4 (17.4%) |
| NA                                    | 17 (23.6%) | 9 (18.4%) | 8 (34.8%) |
| **Dedifferentiated component**        |       |               |            |
| Osteosarcoma                          | 26 (36.1%) | 20 (40.8%) | 6 (26.1%) |
| UPS                                   | 26 (36.1%) | 20 (40.8%) | 6 (26.1%) |
| Fibro/myofibroblastic sarcoma         | 11 (15.3%) | 8 (16.3%) | 3 (13.0%) |
| Undifferentiated spindle cell sarcoma | 10 (13.9%) | 5 (10.2%) | 5 (21.7%) |
| Rhabdomyosarcoma                      | 2 (2.8%) | 1 (2.0%) | 1 (4.3%) |
| Angiosarcoma                          | 1 (1.4%) | 1 (2.0%) | 0 (0.0%) |
| **Size of dedifferentiated component**|       |               |            |
| Microscopic                           | 11 (15.3%) | 8 (16.3%) | 3 (13.0%) |
| Macroscopic                           | 61 (84.7%) | 41 (83.7%) | 20 (87.0%) |
| **Chemotherapy**                      |       |               |            |
| Surgery                               | 47 (65.3%) | 32 (65.3%) | 15 (65.2%) |
| Radiation                             | 4 (5.6%) | 1 (2.0%) | 3 (13.0%) |
| Radiation > surgery > radiation       | 6 (8.3%) | 6 (12.2%) | 0 (0.0%) |
| Surgery > radiation > radiation       | 5 (6.9%) | 4 (8.2%) | 1 (4.3%) |
| Surgery                               | 8 (11.1%) | 6 (12.2%) | 2 (8.7%) |
| No surgery or radiation               | 2 (2.8%) | 0 (0.0%) | 2 (8.7%) |
| **Surgical margin**                   |       |               |            |
| R0                                    | 53 (73.6%) | 39 (79.6%) | 14 (60.9%) |
| R1                                    | 2 (2.8%) | 2 (4.1%) | 0 (0.0%) |
| R2                                    | 11 (15.3%) | 7 (14.3%) | 4 (17.4%) |
| No surgery                            | 6 (8.3%) | 1 (2.0%) | 5 (21.7%) |

AJCC, American Joint Committee on Cancer, 7th edition; NA, not available; UPS, undifferentiated pleomorphic sarcoma.

exact test for categorical variables and Student t test or Mann–Whitney U nonparametric test for continuous variables. The estimated overall survival (OS, defined as the time from diagnosis to death from any cause), progression-free survival (PFS, the time from diagnosis to progression or death), local relapse-free survival (LRFS, the time from diagnosis to the first local relapse after treatment or death from any cause), and metastasis-free survival (MFS, the time from
from diagnosis to the first metastatic relapse after treatment or death from any cause) were derived using the Kaplan–Meier method and compared by the Mantel-Cox log-rank test. The multivariate Cox proportional hazard model was used to investigate significant prognostic factors. The statistical analyses were performed using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp, Armonk, NY). Kaplan–Meier survival curves were generated in R (version 3.4.1; http://www.r-project.org), using the "survminer" package and the "ggsurvplot" function. All reported P values were two-sided. The level of significance was set at P < 0.05.

3. Results

The median follow-up was 13 months (range: 1–227 months). The OS rates for all patients were 54.9% (95% confidence interval (CI): 43.1%–66.7%) at 1 year, 35.6% (95% CI: 24.1%–47.2%) at 2 years, and 19.2% (95% CI: 9.0%–29.5%) at 5 years. The median OS for all patients was 13.9 months (95% CI: 6.4–21.5 months). The median OS for patients without metastasis at diagnosis versus those who presented with metastases was 22.6 months (95% CI: 2.0–43.1 months) vs. 6.6 months (95% CI: 6.1–7.1 months) with 68.8% (95% CI: 55.4%–82.1%) vs. 26.1% (95% CI: 7.8%–44.4%) being alive at 1 year and 46.6% (95% CI: 31.9%–61.3%) vs. 13.0% (95% CI: 0%–27.1%) at 2 years following diagnosis, respectively (P < 0.001, Figure 2(a)). The 1-, 2-, and 5-year PFS rates in all patients were 33.8% (95% CI: 22.6%–45.0%), 27.7% (95% CI: 16.9%–38.4%), and 21.6% (95% CI: 11.2%–32.1%), respectively.

On univariate analysis, the presence of distant metastasis at diagnosis (P < 0.001, Figures 2(a) and 2(b)), pathological fracture (P < 0.001), lymph node involvement (P < 0.001 for OS, P = 0.040 for PFS), and positive surgical margin or no surgery (P = 0.015 for OS, P = 0.028 for PFS) were associated with poorer OS and PFS, while size of dedifferentiated component (P = 0.038) also correlated with PFS. There was no difference in OS or PFS based on age, gender, site, tumor size, grade, or RT (Table 2). On multivariate analysis, pathological fracture (hazard ratio (HR): 2.77, 95% CI: 1.53–5.03, P = 0.001), tumor size larger than 8 cm (HR: 3.43, 95% CI: 1.73–6.79, P < 0.001), lymph node involvement (HR: 5.27, 95% CI: 1.26–22.08, P = 0.023), metastasis at diagnosis (HR: 5.31, 95% CI: 2.63–10.74, P < 0.001), extraosseous extension (HR: 5.24, 95% CI: 1.11–24.70, P = 0.036), and UPS component (HR: 2.44, 95% CI: 1.31–4.57, P = 0.005) correlated with worse OS, whereas surgical resection (HR: 0.21, 95% CI: 0.08–0.55, P = 0.002) and chemotherapy (HR: 0.23, 95% CI: 0.12–0.44, P < 0.001) were associated with improved OS. Pathological fracture (HR: 2.97, 95% CI: 1.66–5.30, P < 0.001), metastasis at diagnosis (HR: 5.21, 95% CI: 2.73–9.95, P < 0.001), and chemotherapy (HR: 0.43, 95% CI: 0.24–0.77, P = 0.005) were also found to be significant prognostic factors for PFS (Table 3).

Among the 25 patients who received chemotherapy, AP was significantly associated with improved PFS (median: 26.3 vs. 6.4 months, P = 0.007) but not OS. There was no difference in OS or PFS based on osteosarcoma component, UPS, or other regimen received, e.g., methotrexate, MAP, ifosfamide, or IE. Cox multivariate analysis revealed that chemotherapy with AP (HR: 0.29, 95% CI: 0.10–0.80, P = 0.018) correlated with decreased risk while metastasis at diagnosis (HR: 7.12, 95% CI: 1.18–42.89, P = 0.032) showed increased risk for PFS.

Among the 49 patients without metastasis at diagnosis, 17 (34.7%) developed a local recurrence. The 1-, 2-, and 5-year LRFS rates were 75.3% (95% CI: 62.3%–88.2%), 66.2% (95% CI: 53.0%–79.4%), and 56.8% (38.8%–74.8%), respectively. Among the 25 patients who received chemotherapy, AP (HR: 0.23, 95% CI: 0.12–0.44, P < 0.001) correlated with decreased risk while metastasis at diagnosis (HR: 4.13, 95% CI: 1.32–12.77, P = 0.014) was significantly associated with worse LRFS, whereas surgical resection (HR: 0.21, 95% CI: 0.08–0.55, P = 0.002) and chemotherapy (HR: 0.23, 95% CI: 0.12–0.44, P < 0.001) were associated with improved LRFS. Pathological fracture (HR: 2.97, 95% CI: 1.66–5.30, P < 0.001), metastasis at diagnosis (HR: 5.21, 95% CI: 2.73–9.95, P < 0.001), and chemotherapy (HR: 0.43, 95% CI: 0.24–0.77, P = 0.005) were also found to be significant prognostic factors for LRFS (Table 3).

Figure 1: Anatomic sites of dedifferentiated chondrosarcoma.
pathological fracture ($P = 0.017$) and size of dedifferentiated component ($P = 0.017$, Figure 2(d)) correlated with MFS, whereas only macroscopic dedifferentiated component was found to be a significant factor for MFS (HR: 7.78, 95% CI: 1.06–57.17, $P = 0.044$) by the multivariate analysis (Table 4).

### 4. Discussion

The majority of literature investigating prognostic factors affecting DDCS survival were reports on small cohorts from single centers, and only a few more recent ones reported data collected from multiple centers or a large nationwide

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**Figure 2:** Kaplan–Meier curves. (a) Overall survival and (b) progression-free survival in patients with dedifferentiated chondrosarcoma with and without metastasis at diagnosis. (c) Local relapse-free survival in patients with nonmetastatic dedifferentiated chondrosarcoma according to surgical margin. (d) Metastasis-free survival in patients with nonmetastatic dedifferentiated chondrosarcoma according to the size of dedifferentiation.
Table 2: Prognostic factors for overall survival and progression-free survival in all patients with dedifferentiated chondrosarcoma by univariate analysis.

| Variable                              | Overall survival (months) | Progression-free survival (months) |
|---------------------------------------|---------------------------|------------------------------------|
|                                       | Median 95% CI P           | Median 95% CI P                    |
| Overall                               | 13.9 6.4–21.5 0.322       | 6.6 3.7–9.4 0.424                  |
| Age                                   |                           |                                    |
| ≤60 years                             | 14.2 5.8–22.5 0.422       | 8.4 6.5–10.4                       |
| >60 years                             | 12.3 1.7–22.9 0.422       | 5.4 3.8–7.0                       |
| Gender                                |                           |                                    |
| Female                                | 11.8 7.8–15.9 0.445       | 5.9 3.6–8.2                       |
| Male                                  | 19.0 8.1–29.9 0.445       | 8.0 4.9–11.2                      |
| Pathological fracture                 |                           |                                    |
| No                                    | 22.6 0–46.1 0.001         | 9.2 0–21.1 0.001                  |
| Yes                                   | 7.0 4.6–9.4 0.001         | 4.0 2.3–5.8                       |
| Site                                  |                           |                                    |
| Extremity                             | 11.8 7.8–15.9 0.304       | 6.1 4.3–7.9                       |
| Axial                                 | 19.0 9.6–28.4 0.304       | 9.0 6.6–11.3                      |
| Tumor size                            |                           |                                    |
| ≤8 cm                                 | 21.9 15.4–28.4 0.168      | 8.4 4.5–12.3                      |
| >8 cm                                 | 11.3 8.1–14.4 0.168       | 6.4 4.6–8.2                       |
| Discontinuous                         | 8.5 0–41.8 0.168          | 1.4 0–108.6                       |
| Lymph node involvement                |                           |                                    |
| No                                    | 14.2 6.6–21.7 0.001       | 7.2 4.5–9.8                       |
| Yes                                   | 4.7 1.8–7.6 0.001         | 4.0 2.1–5.9                       |
| Distant metastasis                    |                           |                                    |
| No                                    | 22.6 2.0–43.1 0.001       | 10.2 0.1–20.2                     |
| Yes                                   | 6.6 6.1–7.1 0.001         | 4.0 2.6–5.5                       |
| Grade                                 |                           |                                    |
| G2                                    | 27.4 0.2–54.6 0.323       | 17.8 0–76.7                       |
| G3                                    | 12.3 9.1–15.5 0.323       | 6.4 4.6–8.2                       |
| AJCC stage                            |                           |                                    |
| II                                    | 22.6 2.8–42.4 0.001       | 10.2 0–21.4                       |
| III                                   | 8.5 0–41.8 0.001          | 1.4 0–108.6                       |
| IV                                    | 6.6 6.1–7.1 0.001         | 4.0 2.6–5.5                       |
| Extraosseous extension                |                           |                                    |
| No                                    | 58.9 56.9 0.108           |                                    |
| Yes                                   | 12.8 8.9–16.6 0.108       | 6.4 3.9–8.9                       |
| Lymphovascular invasion               |                           |                                    |
| No                                    | 14.2 0.8–27.6 0.128       | 8.4 5.2–11.5                      |
| Yes                                   | 15.1 0–38.7 0.128         | 5.7 0.8–10.7                      |
| NA                                    | 10.3 3.3–17.4 0.128       | 5.1 2.0–8.1                       |
| Osteosarcoma component                |                           |                                    |
| No                                    | 12.3 6.7–17.9 0.801       | 6.6 2.7–10.4                      |
| Yes                                   | 19.0 5.2–32.8 0.801       | 6.4 3.6–9.2                       |
| UPS component                         |                           |                                    |
| No                                    | 14.2 4.3–24.0 0.908       | 6.1 4.6–7.6                       |
| Yes                                   | 12.8 3.4–22.2 0.908       | 8.8 4.1–13.5                      |
| Size of dedifferentiated component    |                           |                                    |
| Microscopic                           | 27.4 0–70.4 0.172         | 56.9 0–147.8                      |
| Macroscopic                           | 12.3 8.5–16.0 0.172       | 6.1 4.8–7.4                       |
| Surgical margin                       |                           |                                    |
| R0                                    | 19.1 8.5–29.8 0.015       | 8.4 5.5–11.3                      |
| R1/R2                                 | 12.3 6.1–18.5 0.015       | 6.6 4.2–9.0                      |
| No surgery                            | 6.6 1.5–11.7 0.015        | 3.2 1.7–4.8                      |
| Surgery                               |                           |                                    |
| No                                    | 6.6 1.5–11.7 0.056        | 3.2 1.7–4.8                      |
| Yes                                   | 15.1 8.1–22.0 0.056       | 8.0 5.5–10.6                      |
| Radiation therapy                     |                           |                                    |
| No                                    | 13.1 8.7–17.6 0.787       | 7.2 4.6–9.8                      |
| Yes                                   | 14.2 0.6–27.7 0.787       | 5.9 1.4–10.4                      |
Despite significant breakthroughs in cancer therapeutics over the past few decades, the prognosis of this aggressive cancer remains dismal, with a 5-year survival rate ranging between 0% and 29%. Our series had a similar 5-year OS of 19.2% (95% CI: 9.0%–29.5%). Consistent with what has been reported in the literature, DDCS was slightly more frequent in males with a median age of 60.5 years in our cohort. Compared to conventional chondrosarcoma, the older age in DDCS is probably due to the slow indolent process of dedifferentiation, which also makes distant metastasis more likely to be present at diagnosis. DDCS are associated with a high rate of pathological fractures [4, 6], which increases the risk of local recurrence and predicts poor survival in some studies [6, 25]. In our series, we observed a similar rate of pathological fracture (38.9%) and a negative impact of pathological fracture on both overall survival and disease progression. It is assumed that pathological fracture could lead to local dissemination of tumor cells through hematoma and the difficulty in achieving wide surgical margins in tumor resection [25]. Indeed in our series, R0 resection was achieved in only 54% of all patients with pathologic fractures, compared with 86% in those without fractures ($P = 0.010$). The impact of the histological types of dedifferentiation on the prognosis is still debatable [3, 6, 16]. In the current study, although UPS component did not show significant difference in OS by the univariate analysis, it correlated with a higher risk in mortality by the multivariate analysis. It is possible that certain factors might have more correlation with the UPS component. For example, some patients with UPS component might have been treated more aggressively due to the presumed more aggressive nature, resulting in an improved outcome of UPS in the univariate analysis. Other histological components did not show any influence on OS or PFS.

| Variable          | Overall survival (months) | Progression-free survival (months) |
|-------------------|---------------------------|-----------------------------------|
|                   | Median 95% CI | $P$ | Median 95% CI | $P$ |
| Chemotherapy      |              |     |               |     |
| No                | 10.4 5.1–15.8 | 0.205 | 5.5 4.1–6.9 | 0.451 |
| Yes               | 23.3 5.6–41.1 |     | 9.0 6.5–11.4 |     |

AJCC, American Joint Committee on Cancer, 7th edition; CI, confidence interval; NA, not available; UPS, undifferentiated pleomorphic sarcoma.

| Table 3: Prognostic factors for overall survival and progression-free survival in all patients with dedifferentiated chondrosarcoma by multivariate analysis. |
|-----------------------------------------------|
| Variable                        | Overall survival HR 95.0% CI | $P$ | Progression-free survival HR 95.0% CI | $P$ |
|-----------------------------------------------|
| Pathological fracture                | 1.00 1.53–5.03 | 0.001 | 1.00 1.66–5.30 | <0.001 |
| No                              | | | | |
| Yes                             | 2.77 1.26–22.08 | 0.023 | | |
| Tumor size                       | 1.00 | | 1.00 | | |
| $\leq$ 8 cm                     | 1.00 1.53–5.03 | 0.001 | 2.97 1.66–5.30 | <0.001 |
| $>$ 8 cm                      | 3.43 1.73–6.79 | <0.001 | | |
| Discontinuous                   | 3.73 0.96–14.56 | 0.058 | | |
| Lymph node involvement          | 1.00 | | 1.00 | | |
| No                              | 5.27 1.26–22.08 | 0.023 | | |
| Yes                             | 1.00 | | | |
| Distant metastasis              | 1.00 | | | |
| No                              | 5.31 2.63–10.74 | <0.001 | 5.21 2.73–9.95 | <0.001 |
| Yes                             | 1.00 | | | |
| Extrasosseous extension          | 1.00 | | NS | |
| No                              | 5.24 1.11–24.70 | 0.036 | | |
| Yes                             | 1.00 | | | |
| UPS component                   | 1.00 | | NS | |
| No                              | 2.44 1.31–4.57 | 0.036 | | |
| Yes                             | 1.00 | | | |
| Surgical resection              | 1.00 | | NS | |
| No                              | 0.21 0.08–0.55 | 0.002 | | |
| Yes                             | 1.00 | | | |
| Chemotherapy                    | 1.00 | | | |
| No                              | 0.23 0.12–0.44 | <0.001 | 0.43 0.24–0.77 | 0.005 |
| Yes                             | 1.00 | | | |

CI, confidence interval; HR, hazard ratio; NS, not significant; UPS, undifferentiated pleomorphic sarcoma.
**Table 4:** Significant prognostic factors for local relapse-free survival and metastasis-free survival in patients with nonmetastatic dedifferentiated chondrosarcoma by univariate and multivariate analyses.

| Variable | Univariate | Multivariate |
|----------|------------|--------------|
|          | Median (months) | 95% CI | P  | HR | 95% CI | P  |
| Local relapse-free survival | 61.7 | 0.008 | NS | |
| Pathological fracture | | | | |
| No | Not reached | 11.0 | 0–25.5 | 0.024 | NS |
| Yes | Not reached | | | |
| Lymphovascular invasion | | | | |
| No | Not reached | 11.0 | 0–22.3 | 0.024 | NS |
| Yes | Not reached | | | |
| NA | 61.7 | 0–142.4 | | |
| Surgical margin | | | | |
| R0 | Not reached | 1.00 | 0.004 | 0.002 | 0.044 |
| R1/R2 | 10.2 | 1.2–19.1 | 7.51 | 2.51–22.46 | <0.001 |
| No surgery | 61.7 | 1.98 | 0.25–15.99 | 0.520 | |
| Metastasis-free survival | 18.1 | 0.017 | NS | |
| Pathological fracture | | | | |
| No | 31.6 | 0–82.3 | | |
| Yes | 6.4 | 3.1–9.7 | | |
| Size of dedifferentiated component | | | | |
| Microscopic | | | | |
| NA | Not reached | | | |
| Macroscopic | 9.0 | 6.4–11.6 | 1.00 | 7.78 | 1.06–57.17 |

CI, confidence interval; HR, hazard ratio; NS, not significant.

**Table 5:** Studies on the survivorship of dedifferentiated chondrosarcoma cohort since 2000.

| Authors | Year | No. | Mean age (range) | M : F | 5-year OS | Comments |
|---------|------|-----|------------------|------|-----------|----------|
| van Maldegem et al. [22] | 2019 | 34 | NA | 17 : 17 | NA | 4 centers, unresectable DDCS, positive factor: doxorubicin monotherapy |
| Nemecek et al. [9] | 2018 | 33 | 62.2 (22–90) | 16 : 17 | 13.6% | 1977–2015, single center, negative factor: CRP |
| Lex et al. [23] | 2018 | 31 | 55.6 (33–76) | 19 : 12 | NA | 1995–2016, pelvic DDCS, positive factor: wide surgical margin |
| Dhinsa et al. [24] | 2018 | 21 | 64 (35–80) | NA | NA | 2000–2010, DDCS with osteosarcoma as predominant component, positive factor: chemotherapy |
| Strotman et al. [7] | 2017 | 159 | 65.2 ± 14.7 | 83 : 76 | 18% | 2001–2011, SEER database positive factor: chest wall tumor, negative factor: size > 8 cm, metastases, no surgical resection |
| Liu et al. [20] | 2017 | 23 | 50.4 (32–73) | 12 : 11 | 17.4% | 2008–2015, single center, negative factors: axial bone location, lung metastasis, inadequate surgical margin, incorrect diagnosis before surgery, and pathological fractures |
| Albergo et al. [25] | 2015 | 17 | NA | NA | NA | 1970–2012, single center, femoral DDCS negative factor: pathological fracture |
| Kawaguchi et al. [8] | 2014 | 41 | 58 (26–86) | 27 : 14 | 15% | 1986–2010, single center, positive factor: ifosfamide-based adjuvant chemotherapy combined with surgical resection |
| Italiano et al. [26] | 2013 | 42 | NA | NA | NA | 1988–2011, 15 centers, advanced DDCS had higher response to chemotherapy than conventional chondrosarcoma |
| Yokota et al. [18] | 2012 | 9 | 58.6 (37–86) | 4 : 5 | 0% | 1996–2010, single center |
| Staals et al. [27] | 2007 | 18 | 46 (22–74) | 12 : 6 | 29% | 1970–2002, single center, DDCS that arises in osteochondroma, positive factor: wide surgical resection with adjuvant chemotherapy |
| Grimer et al. [6] | 2007 | 337 | Median 59 (15–89) | 179 : 158 | 24% | 1975–2005, 9 centers, negative factors: pathological fracture, pelvic location, increasing age, inadequate margins of excision |
| Staals et al. [3] | 2006 | 123 | 59.2 (24–83) | 66 : 57 | 24% | 1969–2003, single center, surgery recommended |
| Bruns et al. [1] | 2005 | 13 | 59.8 (36–72) | 7 : 6 | 8% | 1990–2003, single center, surgery recommended |
The value of neoadjuvant or adjuvant chemotherapy remains inconclusive, and the majority of retrospective studies did not reveal any benefit [1, 3, 6, 18, 20]. In the current study, similar to the UPS component, chemotherapy showed a significantly decreased risk in mortality and disease progression by the multivariate analysis but not univariate analysis. Some patients with more aggressive factors might have been treated more aggressively with chemotherapy, which might have masked the effect of chemotherapy in univariate analysis. On the other hand, however, the limited data on the response to neoadjuvant chemotherapy in our series only indicated a relative resistance of DDCS to most classical anti-bone sarcoma drugs. Several studies have indicated that ifosfamide-based adjuvant chemotherapy [8] or doxorubicin monotherapy [22] may offer survival benefit for patients with DDCS. In our series, the combination of doxorubicin and cisplatin was found significantly associated with delayed disease progression. However, the analyses were limited due to the small size of the patients who received chemotherapy and the heterogeneity in chemotherapy regimen during the past three decades.

Surgical resection with complete removal of the tumor is important for LRFS and should be attempted whenever possible. This has also been supported by other studies, although the poor prognosis may influence the radicality of the resection, particularly if it associated with significant morbidity [5, 6, 20]. Consistent with other studies, the prognosis is largely determined by the rapid progress of metastases [1, 7, 20]. There are even fewer data on the influence of RT in the literature. We did not observe any difference in the prognosis by RT, including LRFS, even in patients who did not achieve a complete excision of the tumor.

The limitations of this study cannot be ignored, considering the retrospective nature of this study, long time, and heterogeneity in practice of treatment of our cohort due to the rarity of DDCS. The future of research potentially lies in prognostic, multicenter studies.

5. Conclusions

The prognosis of DDCS is poor. Distant metastases are frequently seen either at initial presentation or as later treatment failure. Complete surgical resection remains a significant prognostic factor for local control. Chemotherapy with doxorubicin and cisplatin seems to have better PFS. More prognostic, multicenter clinical trials are warranted to further stratify patients and explore the effectiveness of chemotherapy with both classical anticancer drugs and novel targeted therapies in patients with DDCS.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors report no conflicts of interest regarding the publication of this article.

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