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Dedifferentiation in bone and soft tissue sarcomas: How do we define it? What is prognostically relevant?☆,☆☆

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ABSTRACT

Dedifferentiation traditionally is defined by descriptive criteria as a tumor showing an abrupt change in histology from a conventional, classic, low-grade appearing neoplasm to a tumor that is more cellular, pleomorphic and "high grade", with grading typically being performed by subjective criteria. The dedifferentiated areas range from areas with recognizable histologic differentiation which differs from the primary tumor (such as an osteosarcoma arising from a low-grade chondrosarcoma) to areas containing sarcomas without specific histologic differentiation (such as pleomorphic or spindle cell sarcoma). Many, but not all, dedifferentiated tumors are aggressive and associated with significantly shorter survival than their conventional counterparts, even grade 3 conventional tumors. As a result, dedifferentiated tumors are generally considered to be clinically aggressive and as a result, more aggressive surgery or the addition of (neo)adjuvant chemotherapy is often considered. However, long-term (greater than 20 year) survivors are reported in the most common dedifferentiated bone and soft tissue sarcomas. Moreover, use of mitotic criterion for defining dedifferentiation in dedifferentiated liposarcoma as well as grading (by the French system) have been found to be associated with survival. This paper reviews the literature on dedifferentiated chondrosarcoma, dedifferentiated liposarcoma, dedifferentiated chordoma and dedifferentiated parosteal osteosarcoma. As a result of that review, recommendations are advocated to identify evidence-based, objective diagnostic and grading criteria for dedifferentiation that are appropriate for each tumor type. Adding such criteria will improve consistency in diagnosis worldwide, allow easier comparison of clinical research performed on dedifferentiated tumors and help communicate (to patients and clinicians) the tumors with highest risk of clinically aggressive behavior, to allow appropriate and personalized treatment planning.

1. Introduction

The term "dedifferentiation" was first used in chondrosarcoma by Dahlin and Beabout in 1971(1), although the histologic features of dedifferentiation had been described earlier for chondrosarcoma and as early as 1913 for chordoma [2,3]. Dahlin and Beabout described their dedifferentiated chondrosarcomas (DDCS) as biphasic tumors consisting of low-grade chondrosarcoma adjacent to "… undifferentiated zones of fibrosarcoma or osteosarcoma …". They reported an aggressive clinical course, with 57 % of patients dying within 12 months, compared to a 70 % 5-year survival for typical chondrosarcoma [1].

Following the publication of Dahlin and Beabout's paper, the term dedifferentiation was applied to several other sarcomas including liposarcoma (well-differentiated/dedifferentiated (WD/DDLPS)) [4], chordoma (DD chordoma) [5], parosteal osteosarcoma (DDPO) [6] solitary fibrous tumor [7] and gastrointestinal stromal tumor [8]. As will be described further below, these all used similar, subjective and descriptive criteria as Dahlin and Beabot. The one exception was DDLPS, where Dr. Harry Evans included in the diagnostic criteria the requirement for at least 5 mitoses/10 HPFs [4].

The concept of "low grade" dedifferentiation was introduced by Henricks et al. and Elgar and Goldblum in 1997(9, 10) to describe DDLPS with blander histologic features that clinically behaved as a DDLPS; these reports used descriptive criteria only, and did not include the mitotic criterion originally proposed by Evans. Subsequent papers by Evans (2007) and Graham et al. (2023), which used the original mitotic criterion for DDLPS, challenged the notion of "low-grade" dedifferentiation. These authors found the clinical behavior of tumors not meeting

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mitotic criterion for DDLPS was not significantly different from WDLPS and advocated the term "cellular WDLPS" for tumors with non-lipogenic areas that did not meet the mitotic criterion for DDLPS [11,12].

As a result of the persistent lack of consensus over diagnostic criteria for DDLPS, major academic centers worldwide use different definitions of DDLPS and have published clinical research, including studies of response to specific treatments, that almost certainly include tumors that Evans and Graham et al. would diagnose as cellular WDLPS(13–25). While the current WHO acknowledges that "low-grade dedifferentiated liposarcoma is virtually indistinguishable from cellular well-differentiated liposarcoma", it provides no guidance for pathologists regarding the criteria that may or should be used to differentiate these entities [26]. This becomes very problematic when using the National Federation of French Cancer Centers (FNCLCC) Sarcoma Grading system in DDLPS, since the mere act of defining a tumor as WDLPS or DDLPS can result in histologically identical tumors being classified as French grade 1 or French grade 2 [12]. As noted by Kilpatrick, these inconsistencies make it very challenging to evaluate the existing literature regarding response to treatment and prognosis of DDLPS [27].

While dedifferentiated sarcomas overall have a significantly worse prognosis than their conventional counterparts, prolonged survival (over 20 years) of a subset of patients, as reported in DDCS and DDPO [28–31], raises several different questions. Are descriptive criteria alone suitable to define dedifferentiation, or would addition of objective criteria (such as mitoses, necrosis or other factors) result in a group of tumors with more uniform, reproducible and predictable prognosis? Should "dedifferentiation" be analogous to extremely poor clinical prognosis, or should it be used to reflect histologic features?

This paper will review the definition and use of the term dedifferentiation in DDCS, DDLPS, DD chordoma and DDPO. While dedifferentiated solitary fibrous tumor and dedifferentiated gastrointestinal stromal tumors also are reported and well accepted, there are very few cases of each reported to date and these will not be further discussed. This paper will describe the features of these dedifferentiated bone and soft tissue sarcomas and will review clinical outcome data to understand the prognostic relevance of dedifferentiation. Finally, based on the review of the evidence in the literature, I will provide some recommendations for approaches we can take to improve the reproducibility and clinical significance of a diagnosis of dedifferentiation.

2. Brief review of sarcomas using the term "dedifferentiated"

2.1. Dedifferentiated chondrosarcoma

The concept of dedifferentiated chondrosarcoma (DDCS) is well-accepted, following the initial proposed use of "dedifferentiation" in this tumor by Dahlin and Beabout [1]. DDCS comprise approximately 10 % of central chondrosarcomas and only rarely are reported in peripheral chondrosarcoma. Similar to conventional chondrosarcomas, these most commonly arise in the pelvis, femur, humerus and scapula of older adults [1,31].

While initially dedifferentiation was described as showing features of osteosarcoma or fibrosarcoma, currently, the WHO definition is a "… bimorphic histological appearance of a conventional chondrosarcoma component with abrupt transition to a high-grade, non-cartilaginous sarcoma" and the term dedifferentiation is only used when the conventional chondrosarcoma shows grade 1 or 2 features [26]. The proportion of the dedifferentiated component varies by case and has been reported to be as little as 2 % of the entire tumor to up to 98 % of the tumor mass, with the median being approximately 55 %; the interface between the conventional and dedifferentiated components is abrupt (Fig. 1) [1,31,32].

Osteosarcoma, fibrosarcoma and undifferentiated pleomorphic sarcoma/"MFH" are the most common features in the dedifferentiated component, but there is a wide range of other reported histological features including spindle cell sarcoma, rhabdomyosarcoma, pleomorphic rhabdomyosarcoma, myofibroblastic sarcoma and angiosarcoma [31–33]. Although very uncommon, epithelial dedifferentiation has been reported [34–36]. Similar to conventional chondrosarcoma, IDH 1/2 mutations often are present in the dedifferentiated component and in the few reported cases, the IDH mutations have been identical between the dedifferentiated and conventional components [37,38]. IDH mutations have been used to confirm DDCS with unusual presentations [34,35] and may be helpful in small biopsies where only the DDCS component is sampled (Fig. 2). However, IDH1/2 mutations are reported across the spectrum of cartilaginous neoplasms, from benign chondromas to chondrosarcomas of all grades [38,39], and thus are not specific for DDCS.

The dedifferentiated component typically is not graded [29,32,40], or is graded by descriptive systems [31]. One study that included information on the mitotic rate and percent necrosis of the dedifferentiated portion reported an extremely wide range of mitoses (0–99/10 HPFs) and necrosis (0–80 %), however, did not note if outcome was related to these features [41]. The current definition of DDCS does not include objective criteria, such as a minimal mitotic rate and/or necrosis.

The overall prognosis of DDCS is significantly worse than conventional tumors, even grade 3 chondrosarcoma. Reported 5-year survival for dedifferentiated chondrosarcoma is 7.5–24 %, with median survival ranging from 7.5 to 16.8 months [29,31,32,40]. In contrast, 5 year survival rates for grade 3 chondrosarcoma are 31–77 %, for grade 2 chondrosarcoma are 74–99 % and for grade 1 chondrosarcoma are 87–99 % [26]. About 25 % of patients have distant metastases on initial presentation, and metastases consistently are reported as a risk factor for worse prognosis [29,31,32,40].

Several authors have reported that patients with osteosarcomatous

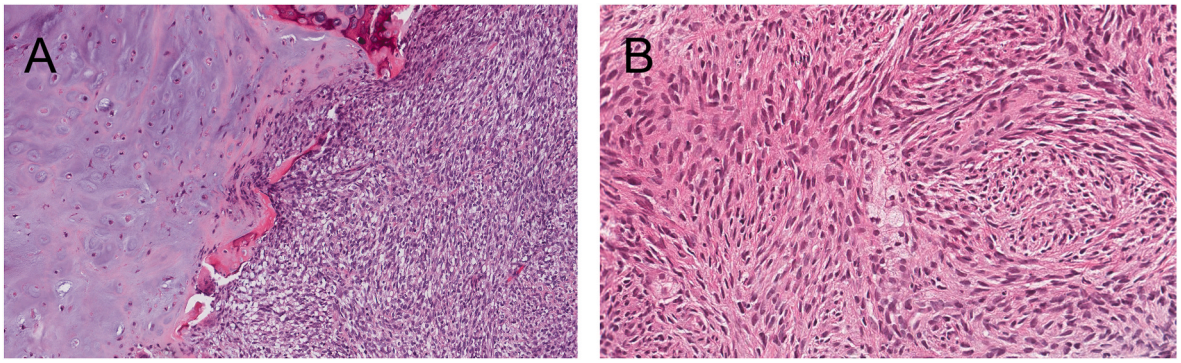

Fig. 1. A. Dedifferentiated chondrosarcoma showing the low-grade conventional cartilaginous tumor adjacent to a highly cellular, high-grade non-cartilaginous tumor. The dedifferentiated area had up to 16 mitoses/10 HPFs as well as necrosis (H&E 10x). B. Lung metastasis from the same patient showing only the dedifferentiated component (H&E 20x).

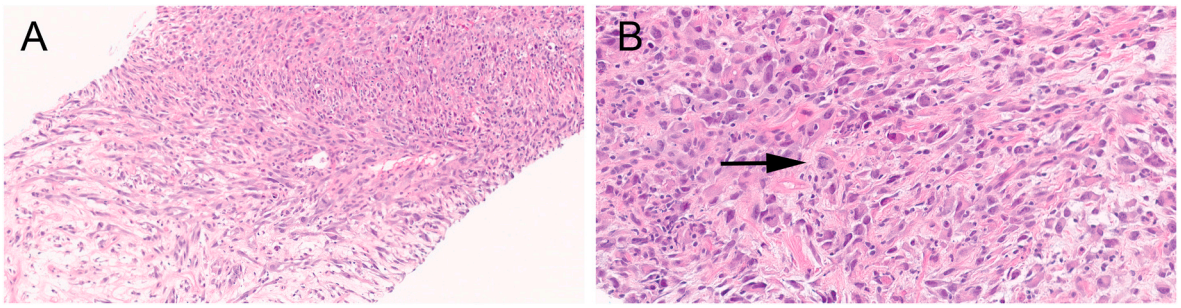

Fig. 2. A. Outside needle core biopsy of a pelvic mass centered in the acetabulum with soft tissue extension. This high-grade tumor shows spindled/myxoid (A, H&E, 10x) and rhabdoid (B, H&E, 20x) features. Mitoses (B, arrow) were 10/10 HPFs and 10 % necrosis was present. Molecular testing demonstrated an IDH1 mutation in Exon 4 (R132C substitution), which is a common finding in chondrosarcoma. Based on imaging, histology and molecular findings, this is most consistent with a dedifferentiated chondrosarcoma with sampling only of the dedifferentiated component.

morphology have better survival than those with fibrosarcomatous or undifferentiated pleomorphic sarcoma/"MFH" histology [29,31]. There are few studies of the impact of the extent of dedifferentiation on prognosis. One large, long-term study reported a significantly better prognosis in patients with less than 50 % dedifferentiated component, however, it is not clear from the paper if this analysis included or excluded patients who presented with metastatic disease [31]. A second, smaller series did not find a difference in survival between cases with dedifferentiation characterized as minimal (<1 cm focus), small (1–2 cm) or large (>2 cm), although case numbers were small in the minimal and small categories and dedifferentiation percentage (ranging from <5 to 10 %) was only reported for the minimal and small tumor groups [41].

Interestingly, a subset of DDCS patients have prolonged survival of close to or more than 20 years [28,29,31]. This data, along with the extremely wide range for mitotic rate and necrosis reported in one study, raises the possibility that the current descriptive criteria are suboptimal for defining dedifferentiation. As patients with DDCS often are treated aggressively, with wide/radical surgical resection and adjuvant or neoadjuvant chemotherapy, inappropriate classification of DDCS risks overtreatment for some patients.

2.2. *Dedifferentiated liposarcoma*

Well-differentiated/dedifferentiated liposarcoma (WD/DDLPS) are common, comprising approximately 9 % of all adult sarcomas [42]. An excellent, detailed review of the history of DDLPS, including the findings of reports using various definitions of DDLPS, was recently published by Kilpatrick [27]. Dr. Harry Evans first proposed the concept of DDLPS in 1979 "… for tumors containing distinct areas of well-differentiated liposarcoma and cellular non-lipogenic spindle cell or pleormorphic sarcoma" and five or more mitoses per 10 high power fields (HPFs) [4].

Henricks and colleagues and Elgar and Goldblum in 1997 expanded this definition to include the concept of low-grade dedifferentiation. These authors proposed this term for WD/DDLPS with non-lipogenic areas that had a low-grade histologic appearance with "… cellularity approaching that of a fibromatosis or low-grade fibrosarcoma and atypia and mitotic activity were low." These authors defined typical (high-grade) dedifferentiation as tumors that "… possessed moderate to marked cellularity and pleomorphism and generally resembled a grade 2 or 3 [malignant fibrous histiocytoma] or fibrosarcoma". These two studies did not find a difference in clinical outcome between the histologically low- and high-grade groups, and they felt the term "low-grade" DDLPS appropriately described both the histologic appearance and clinical outcome. The authors noted "although traditionalists would argue that liposarcomas containing only low-grade dedifferentiation should not be considered DL [dedifferentiated liposarcoma], we disagree with this point of view …" [9,10].

Importantly, Henricks et al. and Elgar and Goldblum did not use the original mitotic criteria of Evans to define either of their DDLPS tumor categories. Subsequent to their reports, Evans in 2007 and Graham et al., in 2023 undertook studies that included identical mitotic criterion (≥5 mitoses/10 HPFs) as a requirement to diagnose DDLPS, and found a difference in survival between tumors with non-lipogenic areas that did and did not meet the mitotic criterion for DDLPS. Furthermore, these authors found no significant difference in survival between classic WDLPS and liposarcomas with non-lipogenic areas with 0–4 mitoses/10 HPFs. They proposed that tumors with non-lipogenic areas that failed to meet minimal mitotic criteria for DDLPS should be classified as cellular WDLPS, since these tumors were more cellular than, yet clinically behaved identically to, typical WDLPS [11,12].

The transition between the WDLPS and DDLPS areas usually, but not always, is abrupt (Fig. 3); rarely these areas are reported to be intermingled [11,16,26]. DDLPS histologically may show diverse features, including undifferentiated pleomorphic sarcoma, myxofibrosarcoma, rhabdomyosarcoma, small round cell sarcoma, spindle cell sarcoma, pleomorphic liposarcoma, osteosarcoma, chondrosarcoma, spindled and pleomorphic cells in a fibromyxoid background, and more rarely angiosarcoma (Figs. 3 and 4). Approximately 40–65 % of DDLPS occurs in the primary tumor [12,16], and tumors with DDLPS can recur as WDLPS [26].

Without using mitotic rate as a criterion for dedifferentiation, there is no objective, reproducible way to differentiate WDLPS and DDLPS. Even the current WHO acknowledges that "low-grade dedifferentiated liposarcoma is virtually indistinguishable from cellular well-differentiated liposarcoma."(26) An example of the high similarity in descriptive, subjective histologic features between some cellular WDLPS and grade 2 DDLPS is shown in Fig. 5. Perhaps because of the challenges inherent in distinguishing WDLPS and DDLPS in the absence of a mitotic criterion, a plethora of definitions of DDLPS have been used in various studies. These include using the original mitotic criterion of ≥5/10 HPFs proposed by Evans [16,19], descriptive criteria only [13,15,17,18,20,24,25], descriptive criteria mentioning mitoses (but not always clear if mitotic criterion were used to define DDLPS) [14,21,22] or no provided definition [23].

Under the FNCLCC grading system, once a tumor is diagnosed as DDLPS, it cannot be graded less than grade 2 [12,43–45]. Thus, a liposarcoma with non-lipogenic areas, 2 mitoses/10 HPFs and no necrosis will be a WDLPS, FNCLCC grade 1, in studies reported by the Milan group and MD Anderson but a DDLPS, FNCLCC grade 2, in most other studies [13,15–20,24,25,43–45]. As noted by Kilpatrick, these inconsistencies make it very challenging to evaluate the existing literature regarding response to treatment and prognosis of DDLPS [27], which in turn risks over- or undertreating patients.

Four large studies from different centers worldwide, using the original mitotic criterion (≥5/10 HPFs) for DDLPS, consistently have found significantly worse survival for DDLPS compared to WDLPS. This includes the original study by Evans (MD Anderson) in 2007, Mussi et al.

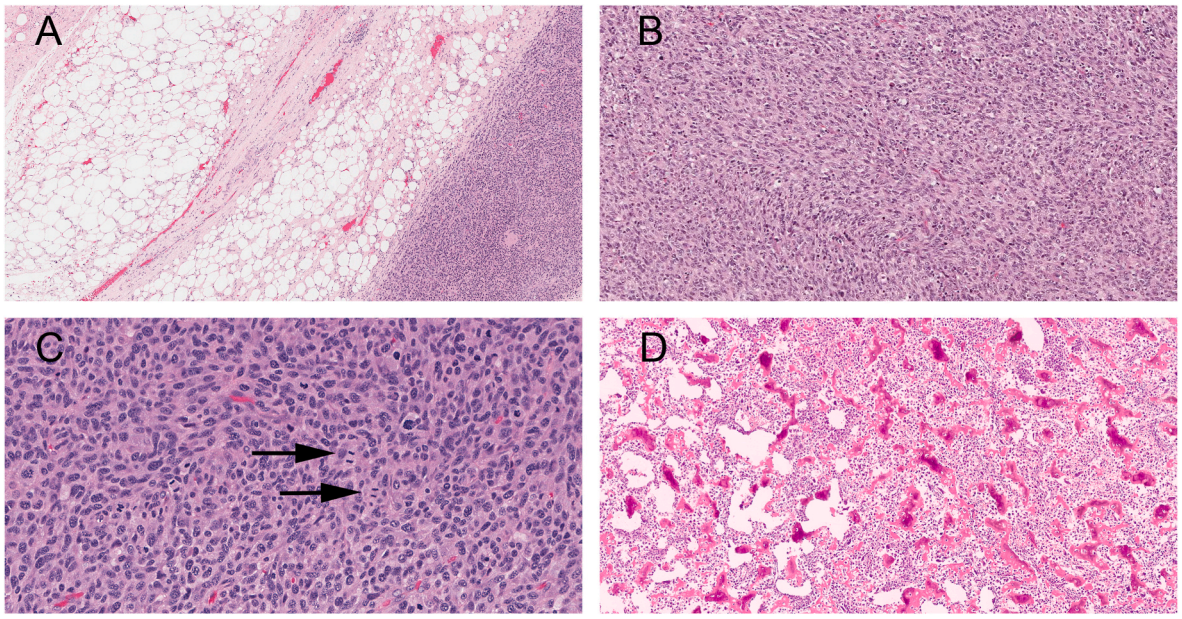

Fig. 3. WD/DDLPS with an abrupt transition (A, H&E, 4x). FNCLCC grade 3 DDPS may show multiple different features, including spindled (B, H&E, 10x), ovoid/epithelioid (C, H&E, 20x) and heterologous osteosarcoma (D, H&E, 4x). Numerous mitoses are seen in C (arrow).

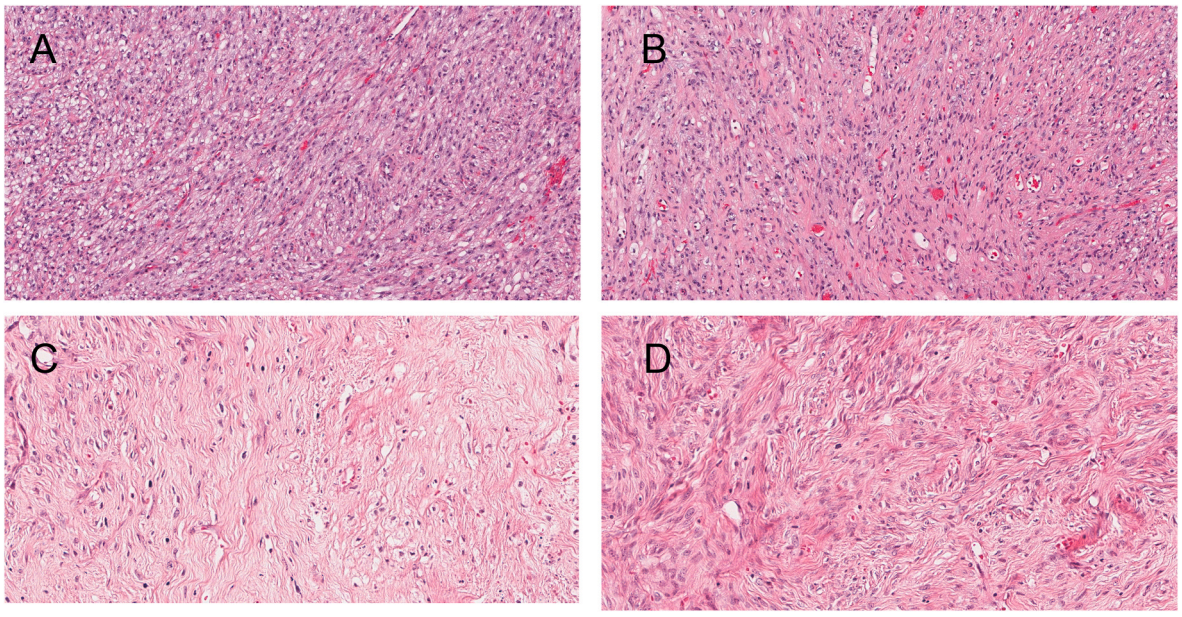

Fig. 4. FNCLCC grade 2 DDLPS showing diverse appearances, including cellular and spindled (A, H&E, 10x), moderately cellular and spindled (B, H&E, 10x) and hypocellular with bland cytology mimicking a cellular WDLPS (C and D, H&E, 20x).

(National Cancer Institute, Milan, Italy) in 2008, Gronchi et al. (National Cancer Institute, Milan, Italy) in 2015 and Graham et al. (UCLA) in 2023. These studies included 61, 93, 114 and 98 patients with follow up of a minimum of 120 months in the Evans study and median follow-up for the other three studies of 71, 68 and 112 months, respectively. These four studies include more than twice the number of patients reported by Henricks et al. and Elgar and Goldblum. It is possible a few of the same patients were included in the Mussi and Gronchi reports, as the study periods overlapped by 2 years.

Grading in DDLPS defined by the original mitotic criterion is significantly associated with survival. Mussi and Gronchi report FNCLCC grade 3 DDLPS had significantly worse survival than grade 2 tumors [16,19]. While Graham et al. did not find an association between FNCLCC grade and survival, they did find poorer survival was correlated with a high mitotic (>20 mitoses/10 HPFs) rate [12]. Studies using mitotic rate as a criterion report median DDLPS survival of 5.5–6.5 years [11,12], but half the patients with FNCLCC grade 3 or a high mitotic rate are dead within 2–3 years [12,16,19].

A subset of DDLPS patients, defined by mitotic criteria, have a more indolent course, with overall survival of 10–20+ years [11,12]. While patients with DDLPS develop metastases more frequently than those with WDLPS, local recurrences more often cause death from disease for both WDLPS and DDLPS [9,10,12,14,19]. DDLPS of central body sites are more aggressive, particularly so for those in a retroperitoneal location [11,26].

Unfortunately, the large number of clinical studies using only

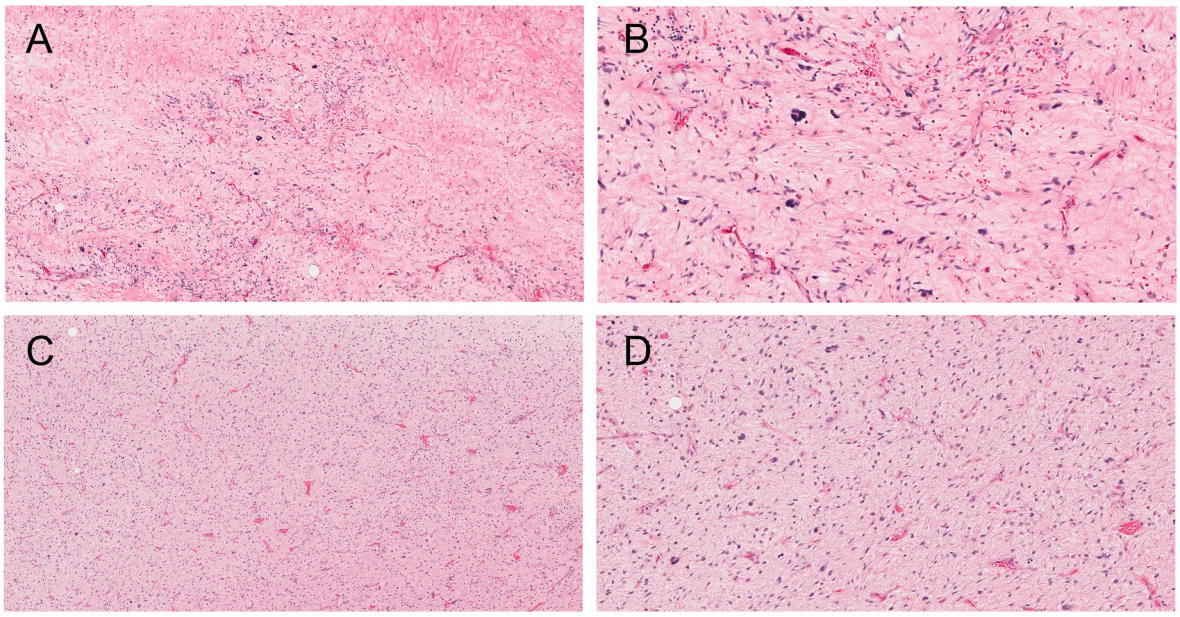

Fig. 5. Cellular WDLPS, showing bland cytology, low to more moderate cellularity and numerous floret-type giant cells (A, H&E, 4x and B, H&E, 10x). FNCLCC grade 2 DDLPS showing bland cytology, relatively low cellularity and numerous floret-type giant cells (C, H&E, 4x and D, H&E 10x). These two tumors demonstrate well the high similarity in descriptive, subjective histologic features between some cellular WDLPSs (mitoses 0/10 HPFs in this case) and grade 2 DDLPSs (mitoses 6/10 HPFs in this case).

descriptive, subjective criterion for the diagnosis of DDLPS are unable to provide any insight as to whether differences in outcome are associated with FNCLCC grade or mitotic rate in the dedifferentiated component [13,15,17,18,20,24,25]. Currently, we do not have data that allows us to predict reliably the DDLPS clinical course for individual patients.

2.3. Dedifferentiated chordoma

In 1913, Debernardi, in an Italian language report, described the histologic features of dedifferentiation in a chordoma, however, the term "dedifferentiated chordoma" first was introduced in 1973 by Heffelfinger and colleagues [3,5]. The WHO defines this as "… a chordoma with a biphasic appearance, characterized by conventional chordoma and high-grade sarcoma." The WHO currently recognizes 3 types of chordoma – conventional, DD chordoma and poorly differentiated. In contrast to DD chordoma, poorly differentiated chordoma lacks a conventional chordoma component, is composed of epithelioid to rhabdoid cells and predominantly occurs in children; immunohistochemically, in addition to being positive for brachyury and cytokeratin, poorly differentiated chordoma characteristically shows loss of INI1/SMARCB1 [26].

DD chordoma is uncommon, and as a result, the literature largely consists of individual or small case reports [3,26]. The few available series report these comprise <1–7 % of all chordomas [3,5,46–48], with the two largest series reporting <1–1.3 % [3,5]. As noted by Hung and colleagues, evaluation of the literature is complicated by multiple different diagnostic terms that have been used inconsistently in the past. For example, poorly differentiated chordoma, anaplastic chordoma and sarcomatoid chordoma are terms that have been used interchangeably with DD chordoma, but "anaplastic chordoma" also has been used for tumors now recognized as poorly differentiated chordoma and "sarcomatoid chordoma" for conventional chordomas with prominent spindling [3]. Similar to conventional chordoma, DD chordoma primarily occurs in the sacrum followed by skull base and while a wide age range is reported (15–81 years old), the median age at presentation is 58 years [3]. The recent literature review by Hung found that 57 % of cases arose de novo in the primary chordoma, 30 % of cases arose following radiation therapy and 13 % arose in a local recurrence; these figures were based on 79 patients with adequate information out of the 87 cases of DD chordoma they identified in the literature [3].

Histologically, the dedifferentiated component typically is described as spindled with appearances of undifferentiated pleomorphic sarcoma, fibrosarcoma or "MFH"; less commonly, tumors with features of osteosarcoma, rhabdomyosarcoma, chondrosarcoma or mimicking malignant peripheral nerve sheath tumor have been reported. DD chordoma may show a gradual transition or intermingling of the dedifferentiated and conventional/chondroid chordoma components [3,49]. Another interesting finding is that metastases may contain only dedifferentiated features, only conventional features or a combination of both, even when the primary tumor did not have any identifiable foci of dedifferentiation [3,49]. DD chordomas typically lose immunohistochemical expression of cytokeratins and brachyury [3,47–50]. TP53 mutations have been identified in 4/6 (66 %) sequenced DD chordomas, however, due to decalcification and age of cases, few cases have been sequenced successfully. In one of the cases with TP53 mutations, the identical mutation was present in the conventional component as well [3,48].

Mitotic rate is reported inconsistently for DD chordomas. Several studies note mitotic rates of at least 15/10 HPFs [48,50] or a "high" mitotic rate (defined as >5/10 HPFs) along with a Ki-67 index of 40 % [46], consistent with a high grade sarcoma; in these same studies, the mitotic rate was significantly lower in the conventional chordoma component (0–4/10 HPFs). One study of 10 cases noted considerable overlap in mitotic count between areas of conventional chordoma (median <1, range <1–26/10 HPFs) and DD chordoma (median 16, range 1–45/10 HPFs) but did not say if outcome was related to mitotic rate [3]. In studies that report on the presence of necrosis, virtually all cases have at least focal necrosis, however, no overall percentage of necrosis is reported [3,48]. The current definition of DD chordoma does not include objective criteria, such as a minimal mitotic rate and/or necrosis.

DD chordomas are highly aggressive tumors and the vast majority are treated with surgery [3,26]. Hung and colleagues, in their literature review, found a median overall survival of 20 months and all patients died within 9 years of diagnosis. Significantly worse survival was seen for tumors arising outside of the sacrum (possibly related to the potential for complete surgical excision) and for tumors not treated with radiation therapy. There were no significant differences in overall survival by

large size (>10 cm) or presentation (de novo, arising in a local recurrence or occurring after radiation therapy). Metastases occurred in 46 % of patients [3]. Chemotherapy does not appear to improve survival significantly. In contrast, conventional chordomas have a median overall survival of 7 years [26]. As with DDCS, the presence of longer-term survivors raises the question of whether objective diagnostic criterion, such as mitotic rate or molecular findings, could improve the ability to predict an individual's clinical course.

2.4. Dedifferentiated parosteal osteosarcoma

DDPO was originally reported in 1984 [6], however, similar to chondrosarcoma and chordoma, the features of DDPO had been described earlier [51]. Although parosteal osteosarcoma is the most common type of surface osteosarcoma, it only accounts for about 4 % of all osteosarcomas. DDPO is not recognized as a distinct tumor by the latest WHO classification, and is described within the parosteal osteosarcoma section as a typical low-grade tumor showing, "… progression to high-grade sarcoma, which can also be referred to as dedifferentiation …" [26].

Between 15 and 43 % of parosteal osteosarcomas are reported to show dedifferentiation [6,30,52,53], with a rate of 16 % and 24.6 % in the two largest series [30,52]. Similar to conventional parosteal osteosarcoma, DDPO most often arises in the femur, tibia and humerus. Dedifferentiation is seen most often in the primary tumor (54–92 % of cases) and while in recurrences it is most common in a first local recurrence, initial presentation as late as the fourth local recurrence has been reported [30,52,53]. The histologic features of the dedifferentiated component include various types of osteosarcoma (most commonly fibroblastic and osteoblastic, less commonly chondroblastic and telangiectatic), fibrosarcoma, and "MFH", with rare reports of malignant giant cell tumor and rhabdomyosarcomatous differentiation (Fig. 6) [52–56]. Metastases are significantly more common in dedifferentiated tumors, and metastases may show conventional, dedifferentiated or both features [30,52,53,57].

Histologic grading of parosteal osteosarcoma, including DDPO, typically is performed by subjective assessment of various features and either the Broders system, which relies on degree of anaplasia, cellularity and nuclear features, or a variation of it is used [6,30,52,58,59]. Of the three largest series of DDPO, one reported mitotic activity in the DDPO component as averaging 12/10 HPFs, compared to an average rate of 1/10 HPFs for the conventional Grade 1 component and 5/10 HPFs for the conventional Grade 2 component. This study did not provide the range of mitoses nor did it evaluate outcome based on mitotic rate in the DDPO component [52]. None of the large series report on the presence of extent of necrosis in the DDPO component.

DDPO has a significantly worse survival. Of the three largest series, two report that during the study period, 50–60 % of patients with dedifferentiation died of disease, compared to 0–2 % of those with conventional parosteal osteosarcoma [52,53]. The third series calculated the 5- and 10-year survival rates as 65 % and 60 % for DDPO versus 96 % (both time periods) for conventional tumors, with a mean follow-up of 12.5 years (range 3 months–60 years) [30]. Surgery alone typically is used for conventional tumors, while chemotherapy may be added for DDPO. Wide surgical margins have been associated with significantly improved disease-free and overall survival in parosteal osteosarcoma, particularly as up to 80 % of local recurrences in one study showed dedifferentiation [30,60]. One study reports that patients

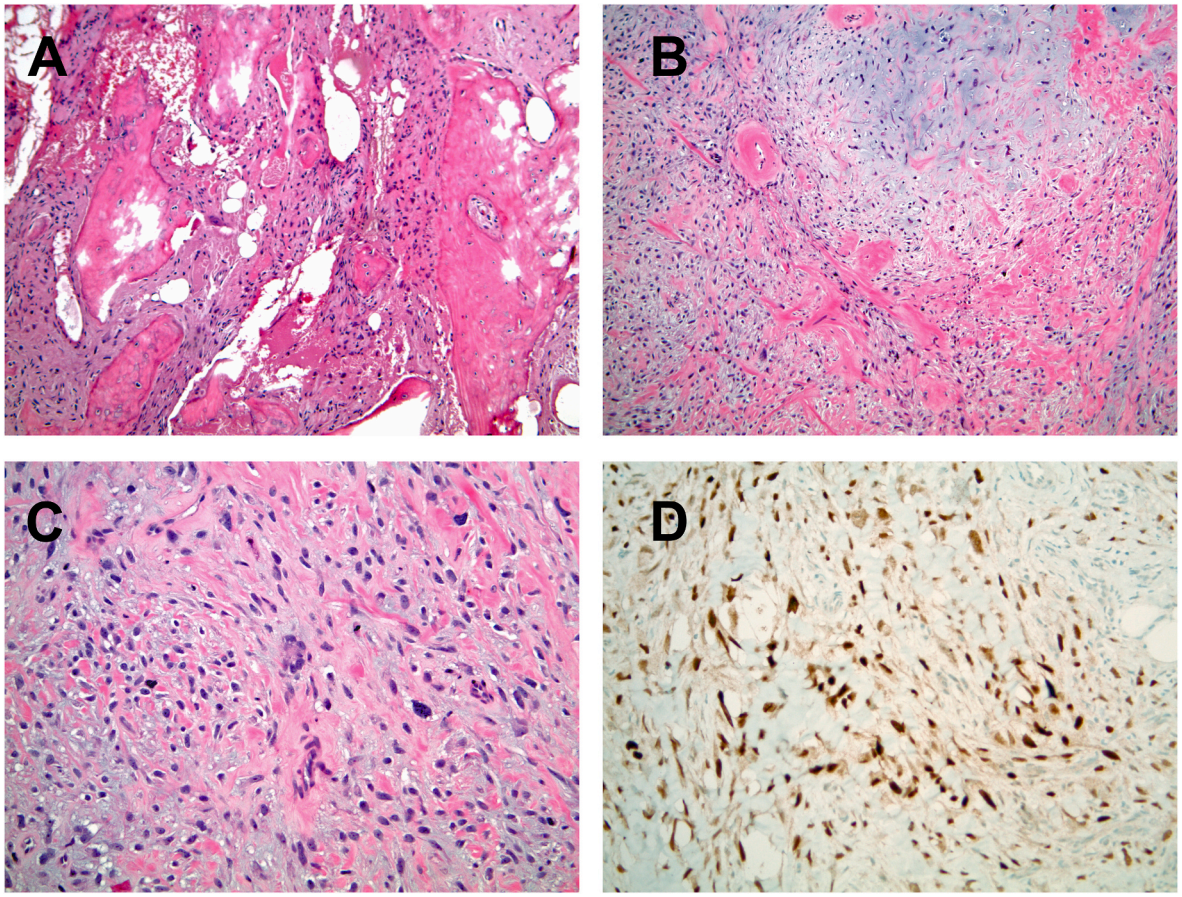

Fig. 6. Dedifferentiated parosteal osteosarcoma showing the low-grade conventional parosteal osteosarcoma (A, H&E, 10x) and the high grade component showing both spindle cell and chondroid features (B, H&E, 10x). The dedifferentiated area (C, H&E, 20x) is positive for MDM2 by immunohistochemistry (D, 20x). (Photos courtesy of Dr. Scott Kilpatrick)

with DDPO and a "good response" (not further defined) to chemotherapy showed significantly longer disease free survival [53], while other studies have not shown a significant impact of chemotherapy on survival [30,60].

As with DDCS, the reported extended survival (60 % at 10 years) in one of the largest series [30], as well as reports of long-term (10–20+ years) in other series [6], suggests that current descriptive histologic criteria for dedifferentiation may not be optimal for identifying the patients most likely to pursue a clinically aggressive course. Chemotherapy may be recommended for DDPO patients, and thus inappropriate classification of DDPO risks overtreatment for some patients. The current definition of DDPO does not include objective criteria, such as a minimal mitotic rate and/or necrosis.

Distinguishing a primary DDPO from a conventional osteosarcoma can be challenging when medullary involvement is present. Approximately 25 % of conventional parosteal osteosarcomas, and 43–60 % of DDPO, involve the medullary space [30,52]. There is no general published consensus regarding the defined limit for medullary involvement in primary DDPO. Two of the larger series set an upper limit for total tumor volume that is intramedullary (25 %) for the tumor to be categorized as parosteal osteosarcoma [30,52] while the third did not indicate any criteria used [53]. MDM2 amplification is more commonly present in parosteal versus conventional osteosarcoma [61,62], however, MDM2 information was present only for a subset of cases from the most recent large series [30] and not available from the two series published in the 1990s [52,53]. Whether 25 % medullary involvement is the appropriate cut-off is unclear. Given the overall excellent prognosis of parosteal osteosarcoma, inappropriate inclusion of conventional osteosarcomas into the category of DDPO risks artificially adversely impacting prognosis data. In this regard, it is important to mention that all three of the larger studies of DDPO report similar rates of distant metastases and death from disease.

3. Summary and recommendations

Dedifferentiation, as originally proposed, indicated an abrupt change in histology from a conventional, classic, low-grade appearing neoplasm to a tumor that was more cellular, pleomorphic and "high grade". The dedifferentiated areas ranged from areas with recognizable histologic differentiation that differed from the primary tumor (such as an osteosarcoma arising from a low-grade chondrosarcoma) to areas containing sarcomas without specific histologic differentiation ("MFH", pleomorphic sarcoma, spindle cell sarcoma, etc.). This is nicely encompassed by Baraban and Cooper's recent proposed conceptual approach to dedifferentiation as "the process by which … a differentiated neoplasm [gives] rise to a morphologically distinct and typically high-grade neoplasm, which is often, but not always, undifferentiated morphologically." [63] While dedifferentiated tumors as a group were found to have a worse prognosis than their conventional counterparts, the clinical outcome in the original reports appeared to be a secondary observation, rather than definitional.

However, today, the diagnosis of dedifferentiation has significant clinical implications, given consistent reports of overall worse survival compared to the conventional counterpart, and even compared to grade 3 conventional tumors. As noted, recommendations for more aggressive surgery or (neo)adjuvant chemotherapy often result from a dedifferentiated diagnosis. Yet, as discussed in sections 2.1, 2.2 and 2.4 above, outcome data also show that a subset of DDCS, DDLPS and DDPO patients have an indolent course with survival greater than 20 years, and 60 % of DDPO patients survive at least 10 years. While survival is not as long in DD chordoma, there are patients with much longer survival (up to 8 years) compared to the average survival of 20 months.

The presence of long-term survivors is problematic for tumors whose names are associated with a more aggressive clinical course than even a grade 3 conventional tumor. As long as we use only subjective diagnostic criteria, there will be continued, considerable variability in the diagnosis of dedifferentiation, even among sarcoma pathology experts/sarcoma centers, and we will continue to see subsets of patients with "dedifferentiated" tumors and long-term survival. Prior literature shows significant interobserver variability in grading bone sarcomas when grade is based on subjective criteria alone (such as cellularity and anaplasia), even among groups of expert orthopedic pathologists [64,65]. In contrast, inclusion of objective criteria, such as mitotic rate and percent necrosis, improves grading systems and in soft tissue sarcomas leads to grades that are significantly associated with prognosis [66].

We must work to identify evidence-based, objective diagnostic criteria for dedifferentiation that are appropriate for each tumor type and can be added to existing subjective criteria so the diagnosis of dedifferentiation is more consistent and reproducible worldwide. Ideally, we also should identify evidence-based, objective criteria to grade dedifferentiation so we can easily communicate (to patients and clinicians) the tumors with highest risk of clinically aggressive behavior, to allow appropriate and personalized treatment planning. There is data supporting the value of FNCLCC grading in DDLPS(16, 19), but not in DDCS, DD chordoma or DDPO and reports of the latter three tumors rarely include information on mitotic rate, necrosis or other objective criteria. As we work towards evidence-based objective criteria for defining and grading dedifferentiation, we may come to realize that some histologic patterns we thought represented dedifferentiation instead are variants of conventional tumors. For example, some chordomas that historically were called "sarcomatoid" or "dedifferentiated" now instead are identified as representing prominent spindling in a conventional chordoma [3]. This will help further refine our diagnostic criteria for dedifferentiation.

Once evidence-based, objective criteria are established, we need to employ those criteria consistently in our research and clinical management, even as we continue to assess if those criteria need modification. And, we need to include these criteria in widely available, commonly used resources for pathologists, to encourage and facilitate their use by all pathologists. We now have 4 large studies of WDLPS/DDLPS, from 3 separate academic centers in the US and Europe, with detailed long-term follow-up, that show the originally proposed mitotic criterion appropriately identifies DDLPS and that DDLPS has a significantly worse survival than WDLPS [11,12,16,19]. The number of patients in these four studies is more than twice the number of patients reported by Henricks et al. and Elgar and Goldblum in 1997 [9,10]. Moving forward, the mitotic criterion of ≥5/10 HFPs should be used to diagnose DDLPS, even as we work to determine if there are ways to improve our criteria, as has been done in other tumors. For example, Evans and colleagues in 1977 proposed including specific mitotic criteria for differentiating grade 1 (0/10 HPFs), grade 2 (<2/10 HPFs) and grade 3 chondrosarcoma (≥2/10 HPFs) and they reported grade was associated with outcome. A subsequent 2009 paper by Eefting and colleagues, with detailed long-term clinical follow-up, found significant interobserver variability in distinguishing enchondroma from grade 1 chondrosarcoma using Evans' mitotic criteria, and reported that adding new criteria (such as host bone entrapment) improved pathologists' performance [67]. As an aside, despite these studies and two additional studies confirming the mitotic criterion in chondrosarcoma correlates with clinical behavior and accurately identifies high grade tumors [68,69], the current WHO does not include specific mitotic criterion and instead notes grade 2 chondrosarcomas have "… the presence of mitoses" and in grade 3 tumors "… mitoses are more easily found …" [26]. And, while the CAP synoptic report includes Evans' original paper as a reference in the explanatory note section for grading, it does not include specific mitotic criterion and instead there is no mention of mitoses in grade 2 chondrosarcoma and for grade 3 states "… contains prominent mitotic activity." [70].

New objective criteria likely will be identified and we must update our diagnostic and grading criteria as this occurs. For example, in the future, recurrent molecular findings may help identify dedifferentiation, or identify dedifferentiated tumors at the highest risk of aggressive

clinical behavior. A molecular study of forty cases of solitary fibrous tumor (SFT) showed two cases with both TP53 and TERT mutations; these were the only dedifferentiated SFTs in this series and the only cases that harbored mutations in both genes [71]. TP53 mutations have also been found in 4 of 6 successfully sequenced DD chordomas, however, the conventional component of one tumor also harbored the same TP53 mutation [3,48]. It is too early to understand if these molecular findings will impact how we diagnose dedifferentiated SFTs or chordomas.

Even objective criterion are imperfect. Reported mitotic rate may be affected by microscopic field size, time to tissue fixation and human factors and identification of necrosis may be impacted by tissue sampling. However, to date, there is strong, repeated evidence that the addition of objective criteria to subjective criteria strengthens grading systems and results in grades that are significantly associated with prognosis [66]. Moreover, pathologists use mitotic criteria in diagnosing and grading many malignancies, mitotic rates can be calculated in both high and low resourced countries and adding mitotic criteria to the diagnosis or grading of dedifferentiation does not require significant time, energy or expense.

In summary, pathologists must accurately and reproducibly diagnose and grade dedifferentiation, to avoid over- or under-treatment of patients and to ensure reproducibility and consistency in clinical trials and clinical research worldwide. To accomplish this, we need to develop updated, evidence-based diagnostic criteria for DDCS, DD chordoma and DDPO that include objective, reproducible histologic criterion/criteria along with traditional subjective/descriptive criteria. We already have objective, evidence-based diagnostic criteria for DDLPS (mitotic rate $\geq$5/10 HPFs) that have been confirmed in large numbers of patients and at multiple centers; these criteria should be adopted uniformly. Once we have evidenced-based diagnostic criteria, we should determine if evidence-based grading criteria will permit more accurate and reproducible correlation with clinical behavior. Together, these efforts will help us better communicate with patients and clinicians the likely clinical behavior of individual tumors, so they can make personalized treatment decisions. To paraphrase Dr. Kilpatrick's recent comments on DDLPS, "If appropriate therapeutic approaches are to be applied to [differentiated sarcomas], there needs to uniform agreement regarding the histologic definition, grading, and staging of [differentiated sarcomas]."(27).

CRediT authorship contribution statement

Sarah M. Dry: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization.

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