

Dedifferentiated Low-Grade Osteosarcoma, Outcome with or Without Chemotherapy: A Systematic Review

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Abstract: The treatment of low-grade osteosarcomas is surgical resection with wide margins. In instances of dedifferentiation, a therapeutic paradigm similar to that of conventional high-grade osteosarcoma has not been adequately evaluated in these neoplasms. The main objective of this review was to define whether the addition of chemotherapy to surgical treatment has an impact on the survival of patients with dedifferentiated low-grade osteosarcomas. Secondary objectives were to observe the degree of histological response to neoadjuvant chemotherapy and to describe the percentage of de novo dedifferentiation. A systematic search of articles including dedifferentiated low-grade osteosarcomas, published between 1980 and 2022 was carried out in the PubMed, Cochrane and Scielo databases. A qualitative synthesis of the results was performed. Twenty-three articles comprising 117 patients were included. The survival of patients treated with surgery alone and surgery with chemotherapy was not statistically significant between the two groups. A good histological response was seen in 20% of specimens treated with neoadjuvant chemotherapy. De novo dedifferentiation was seen in approximately a fifth of low-grade osteosarcomas. The evidence available suggests that the addition of chemotherapy does not have an impact on the survival of patients with low-grade dedifferentiated osteosarcomas.

Keywords: dedifferentiated, osteosarcoma, parosteal osteosarcoma, low-grade central osteosarcoma

Introduction

Dedifferentiated low-grade osteosarcoma is a type of osteosarcoma in which a high-grade sarcomatous component coexists histologically, synchronously or metachronously, with a precursor low-grade osteosarcoma.

From a cytogenetic point of view, low-grade osteosarcomas are characterized by the presence of supernumerary ring chromosomes harboring amplification of chromosomal regions 12q13-q15 that contain the *MDM2* and *CDK4* loci, among other less prevalent genes. The chromosomal alteration translates into overexpression of MDM2 and CDK4 at the protein level, which constitutes the pathogenic and diagnostic mark that is maintained in the progression to a high-grade sarcoma.¹⁻⁵

Based on their intramedullary or juxtacortical location, they are classified as low-grade central osteosarcoma (LGCOS) and parosteal osteosarcoma, respectively.⁶ Together they constitute approximately 6% of all osteosarcomas, being parosteal osteosarcoma twice as common as LGCOS. Low-grade osteosarcomas almost exclusively affect the metaphysis of long bones.⁷

Surgery is the standard treatment for low-grade osteosarcomas and obtaining wide surgical margins that guarantee adequate local control is of utmost importance because a considerable proportion of low-grade osteosarcomas undergo metachronous dedifferentiation during recurrences. Based on the information provided by retrospective studies,⁸⁻¹² however, it is still not clear what should be the optimal treatment for low-grade dedifferentiated osteosarcomas. Currently, a pathology report describing high-grade areas within a low-grade osteosarcoma, even in the absence of

specific guidelines, represents support for the use of chemotherapy in these neoplasms. However, from the available information it can be deduced that the survival impact associated to the addition of chemotherapy to primary surgery of low-grade dedifferentiated osteosarcoma is not entirely evident.

This systematic review seeks to provide a more robust answer to the question of whether the addition of preoperative and/or postoperative chemotherapy to the surgical treatment of dedifferentiated low-grade osteosarcoma provides survival benefit to patients.

Materials and Methods

Bibliographic Search

A systematic bibliographic search was carried out in PubMed, Cochrane and Scielo databases using the following individual and combined search terms: “osteosarcoma”, “Parosteal osteosarcoma”, “Dedifferentiated parosteal”, “dedifferentiated parosteal osteosarcoma”, “Dedifferentiated osteosarcoma”, “Surface osteosarcoma”, “juxtacortical osteosarcoma”, “low -grade central osteosarcoma”, “dedifferentiated low -grade central”, “dedifferentiated central osteosarcoma” and “dedifferentiated low -grade central osteogenic sarcoma”.

The process was carried out following the recommendations of the Preferred declaration reporting items for systematic Reviews and Meta- Analysis (PRISMA).¹³

The search terms were kept as broad as possible and the following filters were used: species (humans), publication date (1980-August 2022), language (English and Spanish).

Eligibility Criteria

Articles that reported or compared the oncological outcome of patients with dedifferentiated low-grade osteosarcomas who met the established PICO (Population-Intervention-Comparison-Outcomes) parameters were included: patients of all ages with dedifferentiated low-grade osteosarcomas with primary and localized disease in the extremities that have received either surgical treatment with non-intralesional margins or that have received pre-operative or post-operative chemotherapy or both. Of note, a marginal surgical margin is not adequate for the treatment of conventional and dedifferentiated low-grade osteosarcomas. The reason for including the cases treated marginally was a pragmatic one to include a larger number of cases in this analysis.

The following types of publications were included in the search: case reports, retrospective case series, clinical trials, observational studies, retrospective cohort analysis. Only studies in English and Spanish and those with available abstracts were considered. The following types of articles were excluded: (1) review articles and monographs; (2) comments on published articles; (3) editorials; (4) conference abstracts or posters; (5) studies focused on animal experiments and in vitro studies with cell lines; (6) studies focused on bioinformatic discoveries; (7) molecular or in situ biomarker studies in fixed, paraffin-embedded tissue samples; (8) ultrastructural studies; (9) studies from which information needed to compare outcomes between intervention and comparison could not be extracted; (10) studies with a population diagnosed as “juxtacortical osteosarcoma” that did not provide radiological and microscopic images that would support the diagnosis of dedifferentiated parosteal osteosarcoma and (11) studies on dedifferentiated low-grade osteosarcomas secondary to Paget’s disease, radiation, or other causes.

Data Extraction

The abstracts of the relevant publications were assessed by two reviewers independently (M.P, R.G). Studies that met the inclusion criteria were selected and those titles and abstracts that implicitly contained exclusion criteria were rejected.

An evaluation form was used to screen the abstracts, which included the general information of the publications, the inclusion and exclusion criteria and the parameters defined in the PICO question. The abstracts that could not be categorically excluded at this stage were included and their full texts assessed for final decision. Discrepancies were resolved by consensus between the two authors. The information extracted from the studies was tabulated in a systematic way in a data extraction spreadsheet. The selected articles had to contain patients with the minimum essential information that would allow us achieving the primary objective of this work. For each study, the following information was

extracted: first author and year of publication, country, type of study, study period, sample size of the study, number of cases in the study sample that met the inclusion criteria, type of treatment (surgery alone/surgery and chemotherapy), oncological outcomes at last follow-up: dead of disease (DOD), not evidence of disease (NED) and the follow-up duration.

Additional information not essential for the primary comparison was extracted from the selected articles and tabulated in the spreadsheet to achieve the secondary objectives. Other variables were the following: general characteristics (age and sex), type of precursor low-grade osteosarcoma, chronology of dedifferentiation (synchronous and metachronous), Enneking stage, largest dimension of the tumor, type of surgery (amputation/disarticulation or limb-sparing surgery), type of negative margin (marginal or wide/radical), timing of chemotherapy (neoadjuvant/adjuvant/both), chemotherapy regimen (drugs), histological response to neoadjuvant treatment (Huvos >90% and <90%).

While reading the complete articles, three retrospective studies were identified^{8,11,14} that were excluded from the analysis of the primary objective because the minimum data necessary could not be extracted from them. These articles, however, were considered for the descriptive results of the secondary objectives, which, therefore, were obtained from a total of 26 articles.

Quality Appraisal

One investigator (M.P) conducted a case report quality appraisal using a modified version of a case report quality assessment tool.¹⁵ The following criteria were used: (1) the publication presents the information of the patients' treatment and outcome in an understandable way (2) the publication provides an unambiguous diagnosis according to updated classification (3) the publication presents histological and radiological evidence that supports the diagnosis.

Data Synthesis and Analysis

The primary outcome of this study is survival. Secondary objectives are proportion of good histologic response to chemotherapy and de novo dedifferentiation.

Data were qualitatively synthesized using descriptive statistics with means and ranges for continuous variables and percentages for dichotomous variables.

Survival was estimated for those patients within the studies in which the follow-up information was presented, using Kaplan-Meier method. Log rank test was used to compare survival curves between the two groups. All statistical tests were two-tailed and a p value <0.05 was considered significant.

Results

Selection of Studies

The systematic literature search yielded a total of 24,388 titles. Of these, 23,909 were excluded due to containing explicit exclusion criteria in the title. 479 titles were selected and, after eliminating duplications, 237 abstracts were included. Of these, 189 were excluded. Lastly, of the 48 studies selected for the complete reading of their texts, 23 manuscripts were included for data extraction. [Figure 1](#) shows the flowchart of the selection process.

Characteristics of the Studies

In total, 23 articles that together contained 117 eligible patients were included. The characteristics of the studies are summarized in [Table 1](#). The manuscripts were published between 1984 and 2020 (1980–1990:5; 1991–2000:6; 2001–2010:7 and 2011–2022:5) and their participants were recruited from 1916 to 2018. Dedifferentiated low-grade osteosarcomas ranged from 1 to 33 in each of the selected papers. Six studies were conducted in Italy,^{10,12,16–19} six in the United States,^{20–25} four in Japan,^{9,26–28} one in each of the following countries: Australia,²⁹ Austria,³⁰ Spain,³¹ Netherlands,³² Indonesia,³³ South Korea³⁴ and one was a multicenter European study.³⁵ Fourteen were retrospective series and nine were case reports.

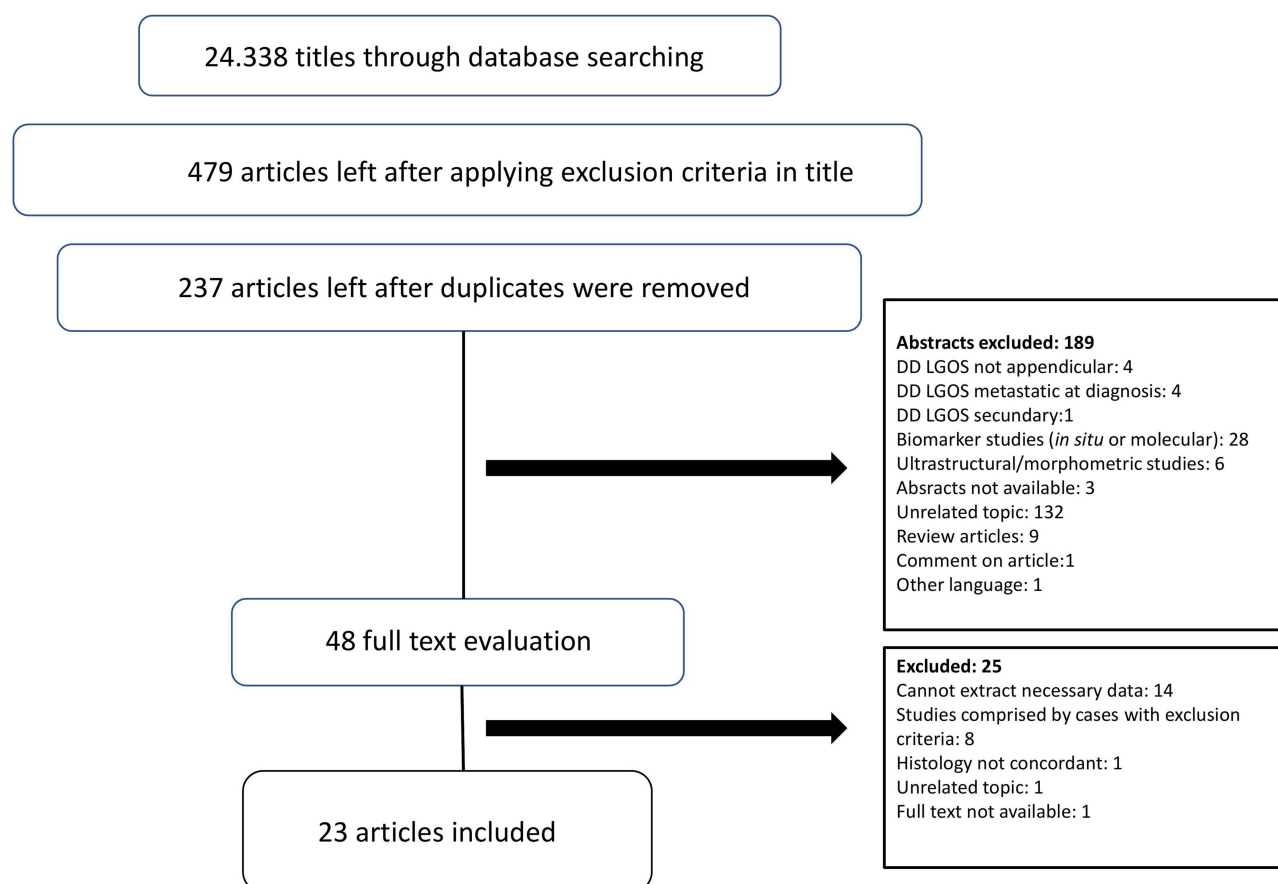


Figure 1 Flowchart of the study selection process.

Quality Evaluation

Most of the articles reported an adequate description of the patients' treatments and outcomes (83%). An unambiguous diagnosis according to the current bone tumors classification and convincing histological and radiological evidence that supported the diagnosis was provided in 87% and 74% of the publications, respectively.

Results of the Objectives

Primary Objective

The clinical data of the patients that fulfilled the inclusion criteria within the studies that were selected is resumed in [Table 2](#). Overall, the 23 articles that were reviewed contained a total of 143 dedifferentiated low-grade osteosarcomas, of which 117 were primaries, located in the extremities, non-metastatic at the time of diagnosis and had been treated surgically with negative margins [wide/radical: 97 (83%); marginal: 10 (8.5%) and unspecified negative margin: 10 (8.5%)]. Thirty-eight (32%) received surgical treatment exclusively and 79 (68%) were treated with surgery and perioperative chemotherapy. Of the latter, 56 (71%) received adjuvant chemotherapy, six (7.5%) neoadjuvant chemotherapy, and 17 (21.5%) were treated with pre- and postoperative chemotherapy.

Seventeen articles included patients who had received some scheme of chemotherapy. Of those, eleven articles, which included patients recruited between 1965 and 2016, specified the therapeutic regimen in a variably detailed manner. In six articles, the details of the chemotherapy regimen were unspecified ([Table 3](#)).

Of 38 patients treated with surgery alone, 29 (76%) had no evidence of disease and six (16%) had died of disease at last follow-up. Of the remaining three, two (5%) were demised of unrelated causes and one (3%) had no follow-up.

Table I Characteristics of the Studies Included in the Analysis

Author/Year	TOS/FU (Months)	#Cases	Surgery Only	SUR + CHT			HR		Surgery Only		SUR+CHT	
				NAD	Adj	Both	< 90%	> 90%	NED/AWD	DOD	NED/AWD	DOD
Toki et al 2019 ⁹	RSC (M:50)	7	0	-	0	7	6	I	na/na	na	5/I	I
Bertoni et al 2005 ¹⁰	RSC (A:107)	16**	6	2	8	-	2	-	5/0	0	7/0	3
Prabowo et al 2020 ³³	RSC (9)	I	I	-	-	-	na	na	I/0	0	na	na
Cardona et al 2008 ²⁰	CR (7)	I	I	-	-	-	na	na	0/0	I	na	na
Sheth et al 1996 ²¹	RSC (M:66)	8	0	0	I	7	4	3	na	na	4/0	4
Kenan et al 1999 ²²	CR (8)	I	0	I	-	-	I	-	na	na	0	I
Azura et al 2009 ¹⁷	RSC (A:61)	3	0	-	2	I	NI	NI	na	na	I/0	2
van Oven et al 1989 ³²	CR (32)	I	0	-	I	-	na	na	na	na	I/0	0
Wines et al 2000 ²⁹	CR (18)	I	0	I	-	-	NI	NI	na	na	0/0	I
Bertoni et al 1985 ¹⁶	RSC (A:24)	6	6	-	-	-	na	na	6/0	0	na	na
Encinas-Ullán et al 2012 ³¹	RSC (NI)	2	0	-	2	-	na	na	na	na	NI	NI
Futani et al 2001 ²⁶	CR (87)	I	0	-	-	I	-	I	na	na	I/0	0
Franchi et al 2004 ¹⁸	CR (6)	I	0	-	I	-	na	na	na	na	0/0	I
Ogose et al 2000 ²⁷	CR (138)	I	0	-	-	I	NI	NI	na	na	I/0	0
Iemoto et al 1991 ²⁸	CR (NI)	I	I	-	-	-	na	na	0/0	I	na	na
Schwab et al 2008 ²³	RSC (M:65)	17	I	-	16	-	na	na	I/0	0	15/0	I
Campanacci et al 1984 ¹⁹	RSC (Min:60)	9*	9	-	-	-	na	na	4/0	4	na	na
Lin et al 2008 ³⁴	RSC (A:106.5)	2	2	-	-	-	na	na	2/0	0	na	na
Ritschl et al 1991 ³⁵	RSC (72)	I	0	-	I	-	na	na	na	na	I/0	0
Lindell et al 1987 ²⁴	RSC (NI)	2	0	2	-	-	NI	NI	na/	na	2/0	0
Funovics et al 2011 ³⁰	RSC (9)	I	0	-	I	-	na	na	na	na	0	I
Pintado et al 1989 ²⁵	CR (11)	I	0	-	I	-	na	na	na	na	I/0	0
Righi et al 2015 ¹²	RSC (M:115)	33**	11	-	22	-	na	na	10	0	18/0	4

Notes: *I patient lost to follow up. **I patient dead of unrelated cause.

Abbreviations: TOS, type of study; FU, follow-up; CHT, chemotherapy; CR, case report; RSC, retrospective series of cases; SUR, surgery; NAD, neoadjuvant; Adj, adjuvant; HR <90% and >90%, histological response/percentage of necrosis in excision specimen; M, median; A, average; Min, minimum; NA, does not apply; NI, no information available; NED, not evidence of disease; AWD, alive with disease; DOD, dead of disease.

Of 79 patients treated with surgery and chemotherapy, 57 (72%) had no evidence of disease and 19 (24%) had died of disease at last follow-up. Of the remaining three, one (1.5%) was alive with disease and two (2.5%) had not been followed up.

The median follow-up- based on 17 articles containing a total of 78 patients with available information- was 73.5 months (Range 4–440; IQR: 24–137). The time interval between surgery and outcome was specified in 21 patients out of 25 that died of disease during the follow up period. The negative outcomes occurred at a median of 15 months (range: 6–36) in patients treated with surgery and at a median of 17.5 months (5–108) in those treated with perioperative chemotherapy and surgery. For patients alive at the time of last follow-up, continuous disease-free survival was prolonged. There were no significant differences in survival between those patients who were treated exclusively with surgery and those who received perioperative chemotherapy [$p=0.51$ ($p < 0.05$)] (Figure 2 and Supplementary Material).

Forty percent of the patients in whom marginal margins were obtained and 68% in whom the margins were wide or radical received chemotherapy. There was no difference regarding the indication for chemotherapy according to the type of negative margins obtained [X^2 (1, $N=107$)] = 3151; $p=0.0759$ ($p < 0.01$).

Within the articles, most of the tumor dimensions were depicted in summary statistics. Twelve patients (10%) had the tumoral size specified.^{9,20,22,25,26,32} The median largest tumor dimension was 10.7 cm. (range 6.5–11.5) Six and five patients with tumors smaller and larger than the median, respectively, received chemotherapy and one patient with a tumor larger than 10.7 cm. did not receive chemotherapy. The indication for the use of chemotherapy seems to have been irrespective of tumor size at least in the small subset of patients with information available.

Table 2 Resume of Clinical Data

Total	117
Margins	
Wide/radical	97 (83%)
Marginal	10 (8.5%)
Not specified	10 (8.5%)
Treatment	
Surgical	38 (32%)
Surgical + chemotherapy	79 (68%)
NAD	6 (7.5%)
Adj	56 (71%)
NAD + Adj	17 (21.5%)
Outcome	Median FU: 73.5 months (Range 4–440)
Surgery only	
NED	29 (76%)
DOD	6 (16%)
Others	3 (8%)
Surgery + chemotherapy	
NED	57 (72%)
DOD	19 (24%)
Others	3 (4%)

Abbreviations: NAD, neoadjuvant; Adj, adjuvant; NED, not evidence of disease; DOD, dead of disease; FU, follow-up.

Table 3 Chemotherapy Schemes

Author	Country	Period	Drugs (Chronology)
Toki et al 2019 ⁹	Japan	1991–2016	API (NAD +ADJ); API (NAD)+ IE-M (ADJ); MAP-I (NAD) + API (ADJ); MAP (NAD) + IM (ADJ); MAP (NAD+ADJ); MAP (ADJ) PA (NAD); M/A/DTIC/I (ADJ)
Sheth et al 1996 ²¹	USA	1980–1992	T-10B
van Oven et al 1989 ³²	Holland	1985	AP (NAD)
Wines et al 2000 ²⁹	Australia	1997	M/PRB/DTIC (NAD+ADJ)
Futani et al 2001 ²⁶	Japan	1993	M (NAD) / PA (ADJ)
Ogose et al 2000 ²⁷	Japan	1986	PA (ADJ)
Ritschl et al 1991 ³⁵	European	1965–1985	AP (NAD)
Lindell et al 1987 ²⁴	USA	1976–1986	MAPI (COSS96) (ADJ)
Funovics et al 2011 ³⁰	Austria	1967–2008	MAVin (ADJ)
Pintado et al 1989 ²⁵	USA	1989	MAPI (ADJ)
Righi et al 2015 ¹²	Italy	1981–2014	

Abbreviations: NAD, neoadjuvant; adj, adjuvant; A, doxorubicin; P, cisplatin; I, ifosfamide; E, etoposide; M, methotrexate; DTIC, dacarbazine; PRB, pirarubicin; V'in, Vincristine.

Secondary Objective

Table 4 summarizes some of the characteristics of the dedifferentiated low-grade osteosarcomas extracted from the 26 articles that were analyzed to achieve the secondary objectives.

All the tumors in this review are high grade and M0, so they all correspond to Enneking II. Undifferentiated low-grade central osteosarcomas were considered IIB when the stage was explicit in the original article or when it could be

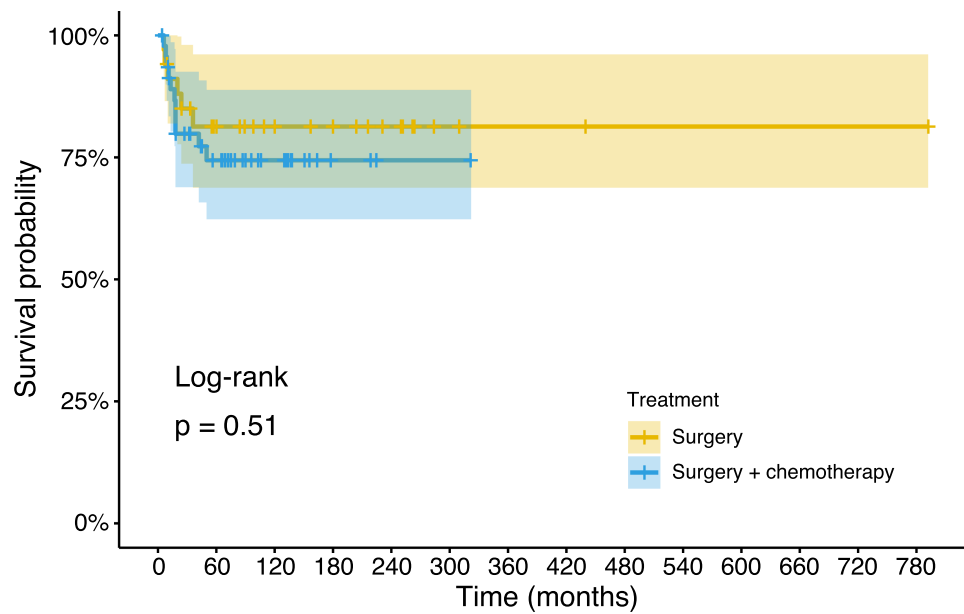


Figure 2 Kaplan-Meier curve comparing survival by type of treatment.

inferred from the information provided in the gross or histological description. Undifferentiated parosteal osteosarcomas were considered IIB as they are extracompartmental by definition. Of 214 high-grade dedifferentiated osteosarcomas, 170 (79%) were stage IIB and in the remaining 44, the extent was neither specified nor could be inferred.

Table 4 Characteristics of the Dedifferentiated Low-Grade Osteosarcomas Analyzed in Secondary Objectives

Clinicopathological Data (n= 214)	
Characteristics	Patients n (%)
Precursor OS	
Parosteal	169 (79)
LGCOS	45 (21)
Enneking Staging	
IIB	170 (79)
NS	44 (21)
Primary Surgery	
Limb salvage	71 (33)
Amputation/disarticulation	12 (6)
NS	131 (61)
Type of margins	
Wide/radical	128 (60)
Marginal	29 (14)
NS/intralesional	7 (3)/50 (23)
Histological response	
Neoadjuvant treatments	40
>90%	8 (20)
<90%	27 (68)
NS	5 (12)

Abbreviations: OS, osteosarcoma; NS, not specified.

Forty patients received neoadjuvant or combined pre and postoperative chemotherapy. Of their resection specimens, 27 (68%) had histologic responses of <90%, eight (20%) had responses of >90%, and in five (12%) the degree of response was not specified.

To have an idea of the proportion of synchronous dedifferentiation in the group of low-grade osteosarcomas, we obtained the proportion of low-grade osteosarcomas with de novo dedifferentiation included in series containing both, low-grade osteosarcomas and osteosarcomas with concomitant dedifferentiation. Of a total of 17 studies, 14 included both conventional low-grade osteosarcomas and low-grade osteosarcomas with high-grade progression. Of a total of 900 low-grade osteosarcomas included in these studies, 186 contained areas of dedifferentiation. Of these, 151 at diagnosis (synchronous) and 35 during recurrences. The proportion of de novo dedifferentiation in conventional low-grade osteosarcomas was approximately 17% (Table 4).

Discussion

This paper reviews the existing literature regarding the survival of patients with dedifferentiated low-grade osteosarcomas treated either with surgery with negative margins or surgery and chemotherapy for localized disease of the extremities. Twenty-three studies with 117 patients were included for the descriptive analysis of the primary objective. All the studies have a level of evidence III.

The median follow-up of the patients in the studies was over 6 years, which we consider adequate since both, local and distant recurrences, are late phenomena in dedifferentiated low-grade osteosarcomas.

The information from the available literature indicates that the addition of cytotoxic perioperative chemotherapy to the surgical treatment of low-grade dedifferentiated osteosarcoma does not affect patient survival. All the information gathered derives from small retrospective series and case reports that comprise heterogenous treatment regimens ranging from intraarterial applications and less effective drugs that have been abandoned to schemes which are comparable to the current standard for perioperative osteosarcoma management, thus for a contextual interpretation of these results, the above information should be considered.

In three of the largest retrospective case series of dedifferentiated low-grade osteosarcomas with direct comparisons of overall survival between patients treated with and without adjuvant chemotherapy^{8,10–12} – the meaning herein used to refer to any combination of agents before or after curative surgery – a survival advantage of perioperative chemotherapy could not be demonstrated.^{8,10,11}

Approximately 70% of the patients in this review that were treated with preoperative chemotherapy showed a rate of induced tumor necrosis of <90%. It was not the objective of this review to correlate the percentage of histological response with the oncological result, however, in the study of Toki et al, dedifferentiated low-grade osteosarcomas showed a poorer histological response than the control cohort of conventional high-grade osteosarcomas, yet the clinical outcome of the former was not markedly different. The foregoing observations suggest that as a group, dedifferentiated low-grade osteosarcomas exhibit a rather disappointing histological response to neoadjuvant cytotoxic chemotherapy and, above all, the level of response is unrelated to the oncological outcome of the patients.

Patients with dedifferentiated low-grade osteosarcomas have a prolonged clinical presentation that can last from several months to even 10 years.^{10,19,21} In this review, 17% of tumors were dedifferentiated at the time of diagnosis, indicating that synchronous dedifferentiation in low-grade osteosarcoma may occur early in approximately one-fifth of patients in the context of a localized disease.

Dedifferentiated low-grade osteosarcomas, although high-grade, are osteosarcomas that affect an older age group and exhibit a biological behavior that is dissimilar to conventional osteosarcoma in terms of late local recurrences, lower rate of distant metastases and longer disease-free survival.^{8,23} Likewise, the cytogenetic basis of dedifferentiated low-grade osteosarcomas, characterized by co-amplifications of *MDM2* and *CDK4* in the 12q13-15 region, is different from the aneuploid and complex karyotypes of conventional high-grade osteosarcomas. *MDM2* is an E3 ligase involved in transporting TP53 to the cytoplasm for degradation³⁶ and *CDK4* is a cyclin-dependent kinase involved in the G1 to S cell cycle transition.³⁷ In low-grade osteosarcomas, levels of mRNA expression of *MDM2* and *CDK4* can reach levels of up to 30 times and 7 times more than basal levels, respectively⁵ translating into protein overexpression.⁴ The effects of *MDM2* and *CDK4* amplification on

TP53 regulation and cell cycle progression, respectively, suggest that overexpression of both genes is necessary for the growth of low-grade osteosarcomas. This makes these tumors potential candidates for targeted therapies with inhibitors of MDM2, CDK4, and selective inhibitors of nuclear transport. However, the progression of low-grade osteosarcomas towards a more aggressive phenotype most likely requires the acquisition of other genetic abnormalities, that are yet to be elucidated to direct research towards the discovery of useful biomarkers. Despite limited data in this regard, the proportion of high-grade component of the tumor has been inquired as a predictive biomarker for benefiting from adjuvant chemotherapy. Righi et al interestingly investigated the impact of the percentage of dedifferentiation on the survival of patients with low-grade central osteosarcomas. In their work,¹² patients with dedifferentiation rates of <50% were found to have high survival rates regardless of whether they received chemotherapy or did not, while patients with resection specimens of tumors with areas of dedifferentiation > 50% had a more aggressive behavior and a lower probability of survival. A single additional study in this review quantifies the proportion of the dedifferentiated component, thus the proportion of dedifferentiation within the tumor as a rationale for the addition of postoperative chemotherapy would be worth exploring further.

This systemic review has several limitations rooted inherently in the very low incidence of dedifferentiated low-grade osteosarcomas resulting in availability of scanty and suboptimal literature. Other limitations are the exclusion of the largest published series due to the unfeasibility of extracting data in line with the pre-established inclusion criteria of our study, the lack of microscopic and radiological evidence supporting the diagnosis of low-grade dedifferentiated osteosarcoma in approximately a quarter of the publications, the unavailability of important information such as tumor size, stage and histological response in an important proportion of the studies, which hampers the comparison by background factors; the inclusion of cases from many dispersed centers in different continents that received heterogeneous treatments during a recruitment period spanning over 100 years inexorably subject this review to chronological and treatment bias.

Conclusion

We conclude that the available evidence does not support the notion that the addition of chemotherapy to surgical treatment has a positive impact on the survival of patients with adequately resected dedifferentiated low-grade osteosarcomas of the extremities. Despite the limitations of this review, we aim that this exhaustive systematic bibliographic search and patient selection work contributes positively to the current debate on the topic raised in the objectives and help as a foundation stone to the search of prognostic and predictive biomarkers in this disease.

Acknowledgments

M.P was supported by the *Sistema Nacional de Investigadores de Panamá (S.N.I) of the Secretaria Nacional de Ciencia y Tecnología (SENACYT)*. We would like to thank Dr. Irene Barrientos Ruiz from *Hospital Universitario La Paz* (Spain), Dr. Ronald Badilla from *Hospital Dr. Rafael Ángel Calderón Guardia* (Costa Rica) and Dr. Amador Goodridge from *Instituto de Investigaciones Científicas y Servicios de Alta Tecnología INDICASAT-AIP* (Panama) for providing valuable comments and suggestions, and Dr. Aaron O'Dea for help producing the figures.

Disclosure

The authors report no conflicts of interest in this work.

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