Experience in the treatment of dedifferentiated chondrosarcoma

A. D. Mitchell, K. Ayoub, D. C. Mangham, R. J. Grimer,
S. R. Carter, R. M. Tillman

From the Royal Orthopaedic Hospital Oncology Service, Birmingham, England

Dedifferentiated chondrosarcoma is a rare, highly malignant variant of chondrosarcoma in which a high-grade spindle-cell sarcoma coexists with a lower-grade chondroid tumour. We have reviewed our experience with this neoplasm in 22 patients, all of whom were treated using modern oncological principles of planned resection and chemotherapy. Despite this the median survival was under nine months and only 18% were alive at five years. Those patients who received chemotherapy, and in whom wide margins of excision were achieved at operation, did best. It is essential to have an accurate preoperative diagnosis in order to plan treatment which may offer a better prospect of cure.

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Chondrosarcomata are usually thought to be low-grade tumours, but up to 11% contain an additional component of high-grade mesenchymal sarcoma¹ which may have features of osteosarcoma, malignant fibrous histiocytoma, fibrosarcoma or anaplastic spindle-cell sarcoma.² The proportion of the tumour which is composed of the less differentiated component varies greatly, to the extent of complete replacement of the cartilage tumour by the more aggressive non-cartilage component. The term dedifferentiated chondrosarcoma was introduced by Dahlin and Beabout³ to describe this variant. They originally reported its presence in low-grade chondrosarcomata, but other authors subsequently described dedifferentiation in higher-grade tumours² and in apparently benign chondromata.¹ An essential histological feature of dedifferentiated chondro-

sarcoma is an abrupt interface between the cartilaginous and non-cartilaginous components, not a gradual merging of tumour types. The hypothesis that the high-grade non-cartilaginous tumour cell line arises in a long-standing low-grade cartilaginous tumour is often supported by the clinical course. Dedifferentiated elements can be found in recurrent chondrosarcoma when the original tumour was completely free from such cells. Alternative hypotheses are either that two malignant cell lines, with different capacities to differentiate, arise simultaneously,^{4,5} or that the non-cartilaginous sarcoma represents malignant transformation occurring in inflamed, but otherwise normal, tissue adjacent to a cartilaginous tumour.⁶

Dedifferentiated chondrosarcoma may have a wide range of radiological appearances. Attempts have been made to identify those features which should raise suspicion of this tumour. A bimorphic radiological pattern was said to be characteristic suggesting that part of the lesion was more aggressive than the rest. Radiographs showing large areas of osseous destruction, without reparative or reactive changes, in association with a large unmineralised soft-tissue mass which occurred in 72% of cases, were suggestive of dedifferentiation.¹ Another classification of dedifferentiated chondrosarcoma distinguishes between those arising centrally and those on the surface of the bone. The central lesions were further subdivided. Type 1 resembles conventional central chondrosarcoma, dedifferentiation being suggested by cortical penetration, a soft-tissue mass, pathological fracture, contrast uptake on angiography, osteochondroma-like ossification and rapid progression. Type 2 shows features of a benign or, at worst, low-grade cartilaginous tumour on which an aggressive malignancy has developed and type 3 has no radiological evidence of a cartilaginous component so that the diagnosis cannot be suspected on purely radiological grounds.⁷

Dedifferentiated chondrosarcoma has a poor prognosis, patients rarely surviving for more than two years.¹⁻⁴ Local recurrence has been reported in up to 50% of cases after excision, with much better control of local disease after radical amputation. Median survival has been as short as six months⁴ and five-year rates of survival as low as 10% to 13%.^{1,7}

We report our experience of treating dedifferentiated chondrosarcoma with the advantages of modern methods of

A. D. Mitchell, FRCS, Senior House Officer

K. Ayoub, FRCS, Registrar

D. C. Mangham, MRCPATH, Consultant Pathologist

R. J. Grimer, FRCS, Consultant Orthopaedic Oncologist

S. R. Carter, FRCS, Consultant Orthopaedic Oncologist

R. M. Tillman, FRCS, Consultant Orthopaedic Oncologist

Royal Orthopaedic Hospital Oncology Service, Woodlands, Northfield, Birmingham B31 2AP, UK.

Correspondence should be sent to Mr A. D. Mitchell at 7 Northland Drive, Scotstoun, Glasgow G14 9BE, UK.

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Table I. Details of the 22 patients with dedifferentiated chondrosarcoma

Case	Age (yr)	Gender	Diagnostic group	Location	Surgery	Survival from diagnosis (wk)	Chemotherapy	Palliative treatment
1	49	M	*	Pelvis (pubis)	EPR†	55		Amputation
2	79	M	2	Humerus	EPR	26	Postoperative	Amputation
3	59	M	3	Humerus	EPR	4		Amputation
4	44	F	1	Femur (proximal)	EPR	199	Postoperative	Excision and chemotherapy
5	60	F	*	Femur (distal)	EPR	32		
6	47	M	1	Femur (proximal)	EPR	390‡	Postoperative	
7	66	M	1	Pelvis (ilium)	None	15		Radiotherapy
8	56	F	1	Femur (distal)	EPR	258‡	Preoperative	
9	17	M	2	Pelvis (ilium)	Amputation	42	Postoperative	
10	37	M	1	Pelvis (acetabulum)	Amputation	37	Preoperative	
11	39	F	1	Pelvis (ilium)	Local excision	164‡	Preoperative	
12	53	M	1	Femur (proximal)	EPR	90‡	Preoperative	
13	38	F	3	Scapula	Local excision	57‡	Postoperative	
14	81	F	3	Tibia	Amputation	48		
15	55	M	3	Femur (proximal)	None	11		
16	56	M	3	Pelvis (ilium)	Curettage	31	Postoperative	Amputation
17	70	M	2	Femur (distal)	EPR	20		
18	61	M	3	Femur (proximal)	None	36		Radiotherapy
19	64	F	2	Femur (proximal)	EPR	36		EPR at second site
20	64	M	3	Femur (proximal)	EPR	37		
21	59	M	1	Pelvis (ilium)	None	0		
22	59	M	2	Humerus	Amputation	3	Preoperative	

* biopsy result not known

† endoprosthetic replacement of resected bone

‡ surviving patients

diagnostic imaging, limb-salvage surgery with endoprosthetic replacement of resected bone (EPR), and adjuvant chemotherapy.

Patients and Methods

A retrospective review was undertaken of all patients with a definitive histological diagnosis of dedifferentiated chondrosarcoma treated by the Royal Orthopaedic Hospital Oncology Service, Birmingham. Since 1977, 22 cases have been identified, representing 7% of 313 patients with chondrosarcoma registered over 20 years. All have been followed up to death or at least for 12 months. Information was obtained from the departmental computerised database, supplemented by review of the case notes. The histological findings were reassessed to ensure that consistent criteria were used in the classification and grading of the tumours.

The intervals from diagnosis to the latest follow-up or death were used in Kaplan-Meier survival analysis, utilising StatView software (SAS Institute Inc, Cary, North Carolina) on Apple Macintosh computers. We examined the effect of age, gender, the site of the tumour, the type of non-cartilaginous component, the type of surgical excision, cytotoxic chemotherapy, and the accuracy of preoperative diagnosis on survival.

Results

The details of patients are shown in Table I. The median survival by Kaplan-Meier analysis was nine months. As

shown in Figure 1 32% (95% confidence interval (CI) 12 to 51) survived to one year and 18% (95% CI 0 to 41) to five years. The longest follow-up without evidence of relapse was 390 weeks. Of 18 patients who had surgical excision local recurrence occurred in nine (50%). Four of these had wide margins of excision and five had intralesional removal. Metastases developed after diagnosis in two patients with an inoperable tumour. After excision of the primary lesion, metastasis, which occurred in ten patients, always involved the lungs; bone was involved in two cases. The mean time from diagnosis to recurrence or metastasis was 32 weeks (2 to 160), and the mean survival with recurrent or metastatic disease was for only nine weeks (0 to 38).

Symptoms and signs. The duration of symptoms before the patient was first seen varied from one week to eight years (mean 59 weeks). The presenting feature was a pathological fracture in five, a swelling in nine and pain only in six. Two patients had a painless swelling. There was no relationship between the prior duration of symptoms and the length of survival after diagnosis.

Age, gender and location. There were 15 men and seven women, aged 17 to 81 years. The mean age at presentation in men was 56.0 years and in women 54.8 years. The age distribution of all chondrosarcomata and those showing dedifferentiation is shown in Figure 2. Dedifferentiation was most often seen in patients in the sixth and seventh decades of life. By contrast, chondrosarcoma in general was seen almost as frequently in the third and fourth decades as in the older age groups. The location of the tumours is shown in Figure 3. The bone most frequently

Fig. 1

Kaplan-Meier graph for all 22 cases of dedifferentiated chondrosarcoma showing survival against time.

Fig. 2

Histogram showing the age distribution of all chondrosarcomata and dedifferentiated chondrosarcomata.

Fig. 3

Frequency of dedifferentiated chondrosarcoma at different skeletal sites for the 22 patients.

affected was the femur (45%), followed by the pelvis (32%). Patients with tumours of the humerus did particularly badly. The difference in survival at two years, 57% in women and 13% in men, was not statistically significant. In patients aged under 55 years at diagnosis the probability of survival at two and five years was 56% (95% CI 19 to 92) and 28% (95% CI 0 to 74), respectively. In those aged over 55 years, 12 out of 13 patients had died within one year.

Radiological appearance. The initial radiographs of 18 patients were available for review. Four tumours were peripheral, arising in a younger subgroup of patients. Applying the classification described above to the central tumours, 64% were type 1, 21% were type 2 and 14% were type 3. Examples of these different appearances are shown in Figure 4. Osteolytic lesions were present in 83%, bimorphism in 72%, cortical perforation in 55%, bone expansion in 27% and pathological fracture in 22%. Soft-tissue masses on plain radiographs were visible in 50%. Serial radiography showed rapid progress of the tumour within the space of a few weeks in six patients. CT or MRI images of the tumour were available in 13 patients. Only two of these showed a soft-tissue mass which could not be seen on the plain films. These findings are shown in Table II and are similar to those reported by others.^{1,7-9}

Fig. 4a

Fig. 4b

Fig. 4c

Fig. 4d

Fig. 4e

Radiographs of typical appearances of dedifferentiated chondrosarcomata showing a) a proximal femoral central chondrosarcoma with cortical destruction, b) and c) an old calcified distal femoral enchondroma with additional features of aggressive malignancy such as osteolysis, pathological fracture and a soft-tissue mass, d) a lytic lesion of the right superior pubic ramus with no radiological signs of chondrosarcoma and e) a peripheral tumour arising on the surface of the proximal humerus with old osteochondromata and a large ossifying soft-tissue mass.

Table II. Radiological features in 18 patients with dedifferentiated chondrosarcoma

Case	Location	Type (Mercuri) ⁷	Osteolysis	Soft-tissue mass		Cortical perforation	Bone expansion	Bimorphism	Pathological fracture
				Radiographs	CT or MRI				
3	Peripheral		No	Yes		No	Yes	Yes	No
9	Peripheral		Yes	Yes	Yes	Yes	No	No	No
11	Peripheral		No	Yes	Yes	No	No	No	No
13	Peripheral		No	Yes	Yes	No	No	No	No
2	Central	1	Yes	Yes		Yes	Yes	Yes	No
4	Central	1	Yes	No	No	Yes	No	Yes	Yes
6	Central	1	Yes	Yes	Yes	Yes	No	Yes	No
10	Central	1	Yes	No	Yes	Yes	No	Yes	No
12	Central	1	Yes	No		No	No	Yes	No
15	Central	1	Yes	No		Yes	No	Yes	Yes
16	Central	1	Yes	No	No	No	Yes	Yes	No
18	Central	1	Yes	No	No	Yes	No	Yes	No
22	Central	1	Yes	Yes	Yes	Yes	Yes	Yes	No
5	Central	2	Yes	No	No	No	No	Yes	Yes
8	Central	2	Yes	No	Yes	No	No	Yes	Yes
17	Central	2	Yes	Yes	Yes	Yes	No	Yes	No
1	Central	3	Yes	No		No	Yes	No	No
7	Central	3	Yes	Yes	Yes	Yes	No	No	No

Fig. 5

Survival against time for groups 1 and 2 (see text).

Table III. Surgical procedures and margins achieved for 18 patients with dedifferentiated chondrosarcoma. The number of local recurrences are given in parentheses

Operation performed	Margins of surgical specimen				
	Radical	Wide	Marginal	Intralesional	Total
Amputation	1	1 (1)	1	1 (1)	4 (2)
EPR*	0	5 (3)	2	4 (3)	11 (6)
Excision	0	1	0	1	2 (0)
Curettage	-	-	-	1 (1)	1 (1)
Total	1 (0)	7 (4)	3 (0)	7 (5)	18 (9)

*endoprosthetic replacement of resected bone

Accuracy of preoperative diagnosis. We classified our 22 patients on the basis of whether the true diagnosis was known before surgical intervention. Group 1 consisted of patients in whom a properly taken biopsy, correctly sited and with the minimum potential to seed tumour into hitherto uninvolved tissue planes, was the only surgical procedure carried out before any operation intended to be curative; the biopsy specimen and radiological features allowed the true diagnosis to be made. Group 2 had operations intended to be curative of malignancy, in an untouched surgical field, but the true diagnosis was not apparent from the preoperative investigations. Group 3 consisted of all those patients who had intralesional excision of tumour or fixation of pathological fractures before the true diagnosis was known, thus risking dissemination of the tumour. An accurate diagnosis before surgery was found to have an effect on survival. Of six patients in group 1 who had an operation four were disease-free at the latest review; survival at two years was 83% (95% CI 54 to 100) and at five years 56% (95% CI 4 to 100). By contrast, all five patients in group 2 died from recurrent disease within one year of diagnosis (Fig. 5). In group 3 survival was poor. Six patients, including two who had no further attempt at tumour excision, died within 37 weeks. The only survivor at more than one year, was a 38-year-old woman with multiple hereditary osteochondromata; dedifferentiated

chondrosarcoma occurred in an osteochondroma of the scapula.

The prognosis in patients who were first seen with a pathological fracture appeared to depend on the initial treatment undertaken. Group 1 included two such patients. One remained free from disease at 258 weeks, the other died from local recurrence at 199 weeks. There was one pathological fracture in group 2 in which the tumour was resected, and one in group 3 in which no further excision was attempted.

Surgical treatment. Four patients presented with inoperable disease or died before surgical excision could be undertaken, in one of a presumed pulmonary embolus within one week. Four patients had amputation as the primary surgical treatment. Limb-salvage surgery with EPR was carried out on 11 patients, at the proximal femur in five, the distal femur in two, the proximal humerus in one and the hemipelvis in one. Two patients had local excision of tumours and chemotherapy. One had curettage and subsequently a local recurrence treated by amputation. The surgical margins achieved and subsequent local recurrences are shown in Table III.

Adjuvant chemotherapy. Cytotoxic chemotherapy was given to five patients before excision of the tumour. In only one was significant (>90%) necrosis achieved. A further six had postoperative chemotherapy. All received doxorubicin

Fig. 6

Survival from diagnosis in patients treated by excision alone and by excision combined with chemotherapy.

and cisplatin as first-line chemotherapy except one elderly patient who had doxorubicin and vincristine. In this group, the probability of survival at five years was 36% (95% CI 0 to 77). The patients who had chemotherapy had a considerably better outcome than those who did not. Excision only, without chemotherapy, was carried out in six patients, all of whom died within one year with a mean survival of under seven months (Fig. 6).

Histological examination. Recognition of the underlying chondrosarcomatous nature of the tumour is of much greater importance than the classification of the dedifferentiated component, since this may behave very differently from the primary sarcoma which it resembles. The dedifferentiated component of the tumour was osteosarcoma in six cases, malignant fibrous histiocytoma in six, leiomyosarcoma in three, malignant giant-cell tumour in two and rhabdoid tumour in one. Survival was not related to the histological appearance.

Discussion

The prognosis of dedifferentiated chondrosarcoma is poor, with a reported median survival of less than six months⁴ and survival at five years of 13%,⁷ with most patients living for less than two years. Our experience of treating this condition with modern diagnostic imaging, limb-salvage and chemotherapy does not show improvement on former methods of management.

Chondrosarcoma, in general, is resistant to chemotherapy, and anti-tumour drugs are rarely used in treatment. It has been suggested that the dedifferentiated component may resemble a high-grade sarcoma in that it is susceptible to chemotherapy,² but published experience does not suggest that chemotherapy is of any benefit. All previous reports, however, are of small numbers of patients and possible benefits may have been obscured by the use of a

wide range of drug regimes within the treatment groups.^{1,4,7} In our small series survival was much better in those receiving adjuvant chemotherapy, usually doxorubicin and cisplatin, than in patients treated by surgery alone, but the number in each group is very small and in a retrospective review of this type, patient selection cannot be excluded as the cause of this difference. When post-chemotherapy specimens were available, the amount of tumour necrosis was low.

Local recurrence occurred with a disappointingly high frequency. Since local control was as likely to occur after limb salvage as after amputation, we consider that limb salvage is an acceptable option when feasible. With the poor rates and short duration of survival for patients with this tumour, preservation of limb function can be offered in the knowledge that amputation gives no greater chance of cure.

It is important to obtain an accurate diagnosis before treatment. Of the patients in whom the true diagnosis was known before excision of the tumour, 50% were free from disease at the latest follow-up, and the two-year survival, from the time of diagnosis, was 63%. With an incomplete preoperative diagnosis there was only one survivor (7%). It appears vital that dedifferentiation is recognised in chondrosarcomata before surgical excision is attempted in order to plan safe margins of resection and to make best use of such adjuvant therapy as may be felt worthwhile. It is important that biopsies are representative of the entire tumour, and that the radiological and clinical features are considered when interpreting tissue specimens.

It is important to maintain a high level of suspicion when investigating and treating chondrosarcoma. The prognosis for patients with dedifferentiated chondrosarcoma was improved by accurate preoperative diagnosis. Every effort should be made to ensure that biopsies are representative of the whole tumour. Locally, this type of sarcoma is very

aggressive and wide margins of excision are of the utmost importance in achieving control of local disease. Adjuvant chemotherapy with cisplatin and doxorubicin was associated with improved survival in a few cases.

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