

Risk factors for survival and local control in chondrosarcoma of bone

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We studied 153 patients with non-metastatic chondrosarcoma of bone to determine the risk factors for survival and local tumour control. The minimum follow-up was for five years; 52 patients had axial and 101 appendicular tumours. Surgical treatment was by amputation in 27 and limb-preserving surgery in 126.

The cumulative rate of survival of all patients, at 10 and 15 years, was 70% and 63%, respectively; 40 patients developed a local recurrence between 3 and 87 months after surgery and 49 developed metastases. Local recurrence was associated with poor survival in patients with concomitant metastases but not in those without.

On multivariate analysis independent risk factors for rates of survival include extracompartmental spread, development of local recurrence and high histological grade. Independent risk factors for local recurrence include inadequate surgical margins and tumour size greater than 10 cm. Location within the body, the type of surgery and the duration of symptoms are of no prognostic significance. Surgical excision with an oncologically wide margin provides the best prospect both for cure and local control in these patients.

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Chondrosarcoma is the most common sarcoma of bone in patients over 20 years of age, with an annual age-specific incidence of 1.7 cases/million population in the UK. It

represents about 25% of all bone sarcoma¹⁻⁴ and typically occurs in adults aged between 30 and 60 years.

The disease has a spectrum of histological differentiation and malignant potential. The distinction between a well-differentiated chondrosarcoma and an enchondroma can be difficult. The latter sometimes has histological features of borderline malignancy, and distinction from a low-grade malignancy may have to be made from the clinical and radiological behaviour of the lesion. Such a benign lesion is sometimes called an 'atypical enchondroma' or 'cartilaginous lesion of unknown malignant potential' to distinguish it from a lesion which is frankly malignant.⁵ The latter may have a highly malignant anaplastic sarcomatous component, referred to as a 'dedifferentiated' chondrosarcoma.^{6,7}

Adequate surgical excision is the most important aspect of management because there is no effective adjuvant treatment available.⁸⁻¹¹ Previous studies have described the natural history, metastatic potential and prognosis.⁸⁻¹³ Many of these extend over several decades and some patients will not have benefited from the advantages of modern methods of evaluation and limb-salvage surgery. The inclusion of benign tumours¹² may affect the prognosis in patients with frankly malignant tumours. Our study evaluates critically the outcome of patients with conventional chondrosarcoma, without metastases at diagnosis, who were treated at a specialist oncology centre.

Patients and Methods

Between 1970 and 1993 we treated 194 patients with localised conventional chondrosarcoma of bone. This series did not include patients with clear-cell or mesenchymal chondrosarcoma, a soft-tissue chondrosarcoma or those with metastases at diagnosis. Forty-one were excluded because of incomplete clinical or histological data, unrecorded follow-up or because they had been referred for advice only, leaving 153 in the study.

The medical records, histological sections and radiographs were reviewed retrospectively. There were 83 men and 70 women with a mean age at diagnosis of 47 years (14 to 80). The mean follow-up period was 93 months (5 to 27). The histological grade was 1 in 76 patients (49%), 2 in 62 (41%) and 3 in 15 (10%). There were 23 patients with

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stage-IA tumours, 53 with stage-IB, 12 with stage-IIA and 65 with stage-IIB, according to Enneking's criteria.¹⁴ In all cases the tumour matrix was entirely chondroid; bone matrix was never produced directly by the tumour cells. Histologically, all tumours showed the features of permeative growth into the host bone in the biopsy sample or in the resected specimen. This is taken as the histological feature which defines a cartilaginous tumour as a chondrosarcoma. The tumours were histologically graded based on cellularity, the characteristics of the tumour matrix, the nuclear features, and the mitotic rate, as recommended by Evans et al.⁸ We excluded tumours which were not clearly malignant. The dimensions of the tumours were measured from the excised pathological specimens.

All patients were fully staged according to the Musculoskeletal Tumour Society staging system.¹⁴ The primary goal of surgery was complete excision of the tumour, with preservation of the limb and its function whenever possible. Amputation was indicated in those cases in which there was neurovascular invasion or in which limb salvage would result in resection of so much tissue as to render the limb functionless. Surgical margins were measured according to the method of Enneking.¹⁴ Like Gitelis et al,⁹ we considered an adequate surgical margin for chondrosarcoma to be uncontaminated, wide or radical. Intralesional, marginal or contaminated margins were regarded as inadequate.

Statistical analysis. The cumulative rate of overall survival and of metastasis-free survival was calculated according to the Kaplan-Meier method.¹⁵ Deaths verified as being from natural causes were considered as censored data. Differences between survival curves were evaluated by the Mantel Cox log-rank test.¹⁶ Multivariate regression tests were performed to identify independent factors which influenced prognosis according to the proportional hazards model of Cox.¹⁷ Fisher's exact tests were used to study differences between nominal data.

Results

The axial skeleton was affected in 52 tumours (34%) and the appendicular skeleton in 101 (66%) (Fig. 1) In patients with grade-1 and grade-2 tumours the median time from the onset of symptoms to diagnosis was 50 and 48 weeks, respectively. Patients with grade-3 lesions presented earlier (median 26 weeks).

The initial surgical treatment was amputation in 27 patients (18%) and limb-preserving surgery in 126 (82%). The excision margins were microscopically negative for tumour in 103 out of 138 patients (75%), but positive in 35. In 15 patients adequate records of surgical or pathological margins were not available to allow determination of the excision margin. These patients were considered to have had inadequate margins. Adequate surgical margins were achieved in 70 patients (wide 63, radical 7), and inadequate margins in 83 (intralesional 35, marginal 33, undetermined 15). Five patients with dedifferentiated chondrosarcoma

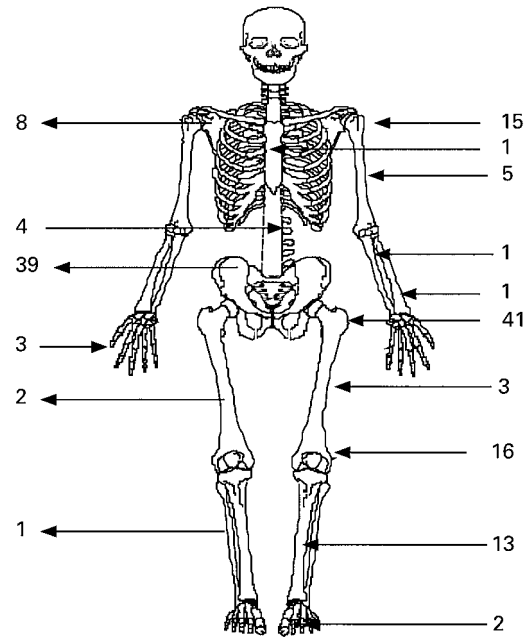


Fig. 1

Diagram showing the location of tumours.

had adjuvant chemotherapy and four had radiotherapy after surgery because of close surgical margins.

The mean diameter of the tumour was 10.8 cm (1 to 30). Records of tumour size were not available in ten patients; 68 tumours were larger than 10 cm and 75 were smaller.

Survival. At the time of review, 100 patients were alive and free from recurrence, five were alive with disease, five had died from causes unrelated to the malignancy and 43 had died from metastatic or progressive growth. The 5-, 10- and 15-year survival rates were 78%, 70% and 63%, respectively. The longest interval from diagnosis to death was 13 years. The histological grade was a significant predictor of survival, as shown in Figure 2. The survival rates at ten years were 89% for grade 1, 53% for grade 2 and 38% for grade 3 ($p < 0.0001$; Table I).

The development of a local recurrence was associated with a significantly worse survival ($p < 0.0001$). The survival rates for patients who developed local recurrence during follow-up were 55% and 32% at five and ten years, respectively, compared with 87% and 84%, respectively, in patients without local recurrence (Fig. 3). The ten-year survival rates for patients with adequate and inadequate margins were 88% and 54%, respectively.

Extracompartmental spread of the tumour was associated with an inadequate surgical margin, local recurrence and poorer survival. The cumulative survival for patients with intracompartmental lesions was 100% at ten years compared with 60% for those with extracompartmental lesions ($p < 0.0001$; Fig. 4). The difference in the survival rates for patients with stage-IIB tumours, with or without local recurrence, was striking. The ten-year survival rate for

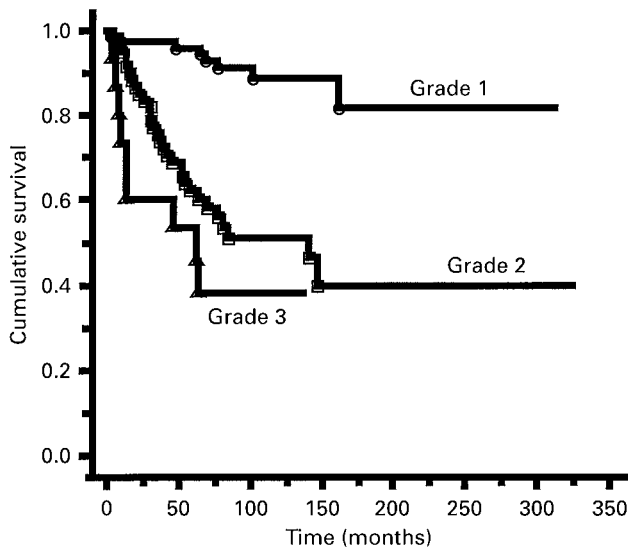


Fig. 2

The overall rate of survival according to histological grade.

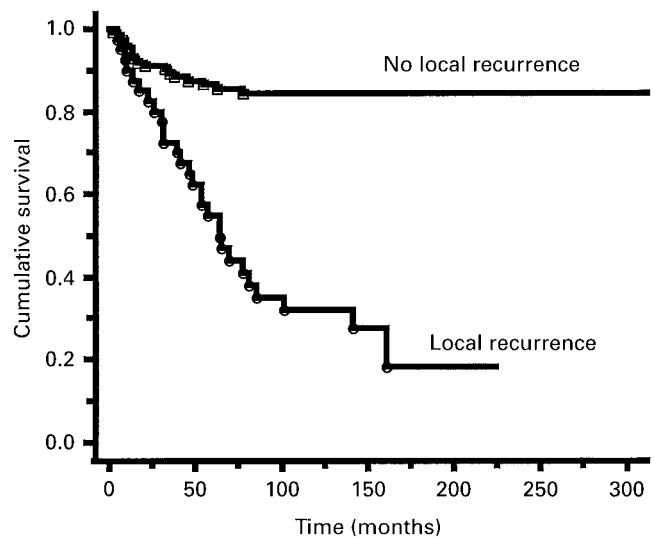


Fig. 3

The influence of local recurrence on the overall rate of survival.

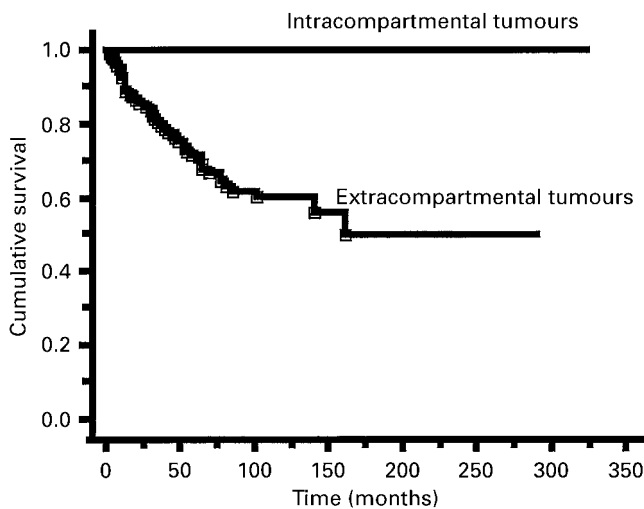


Fig. 4

The influence of extracompartmental spread of the tumour on the rate of survival.

those with stage-IIB tumours without local recurrence was 64% compared with 4% for those with local recurrence ($p < 0.0001$).

The location of the tumour, either in the pelvis or a limb, did not significantly influence survival. The cumulative five- and ten-year survival rates for patients with chondrosarcomata of the pelvis were 69% and 59%, respectively, compared with 81% and 71% for those of the long bones, but the difference was not statistically significant. The survival of patients with stage-IIB tumours who had limb-preserving surgery was similar to those treated by amputation. The size of the tumour had a statistically significant impact on the overall survival. The five- and ten-year survival rates were, respectively, 69% and 55% for

lesions of 10 cm in diameter or greater, and 87% and 83% for lesions of less than 10 cm. There was no relationship between survival rates and duration of symptoms.

Local recurrence and metastases. Local recurrence developed in 40 patients (26%) at a mean time after surgery of 25 months (3 to 87); 22 had pulmonary metastases at the time of diagnosis of a local recurrence, and 18 presented with a local recurrence without metastases. There was a statistically significant relationship between the development of local recurrence and metastases. Overall, 29 of 40 patients (73%) with local recurrence developed metastases compared with 20 of 113 (17%) without.

The factors associated with the development of local recurrence are shown in Table II. Of the 40 patients who suffered this, 34 underwent a second procedure, including further simple excision (16 patients), excision and endoprosthetic replacement (3) and amputation (15). The remaining six patients received palliative treatment because of advanced age and widespread disease. At follow-up, 12 patients who had further surgery were still alive at a mean of 94 months (33 to 196) after reoperation; 22 patients (65%) of the reoperated group died at a mean time of 32 months (1 to 112) after reoperation. Patients with local recurrence who presented with concurrent metastases had a poor prognosis. The cumulative five-year rate of survival after diagnosis of local recurrence was 64% in patients who did not have metastases compared with 5% in those who did ($p = 0.0001$).

Metastases developed in 49 patients (32%) during follow-up. The mean time from primary treatment to the occurrence of metastases was 47 months (4 to 196). The significant factors associated with the development of metastases are shown in Table I.

Multivariate analysis. Multivariate analysis showed that the important risk factors for survival included extra-

Table I. Univariate analysis of the influence of various factors on survival, development of local recurrence and metastases

	Rate of survival (%)		Number with local recurrence (%)	Number with metastases (%)
	5-year	10-year		
Grade				
1 (n = 76)	96	89	16 (21)	10 (13)
2 (n = 62)	62	53*	17 (27)	31 (50)***
3 (n = 15)	53	38***	7 (47)***	8 (53)***
Size (cm)				
<10 (n = 75)	87	83	13 (17)	16 (21)
>10 (n = 68)	69**	55**	26 (39)**	30 (44)**
Margins				
Adequate (n = 70)	90	88	5 (7)	9 (13)
Inadequate (n = 68)	77***	57***	31 (46)***	30 (46)***
Local recurrence				
Yes (n = 40)	55	32	–	29 (73)
No (n = 113)	87***	84***	–	20 (18)***
Compartment				
Intracompartmental (n = 35)	100	100	6 (17)	2 (6)
Extracompartmental (n = 118)	72***	60***	34 (29)	47 (40)***
Site				
Long bones (n = 101)	81	71	23 (23)	30 (30)
Pelvis (n = 52)	69	59	17 (32)	19 (37)
Type of surgery				
Amputation (n = 27)	62	57	6 (21)	1 (41)
Limb salvage (n = 126)	82*	70*	34 (27)	39 (31)

* 0.05 > p < 0.01; **0.01 > p < 0.001; ***0.001 > p < 0.0001

compartmental spread, local recurrence and high histological grade (Table III). The important risk factors for the development of local recurrence included excision with an inadequate margin and tumour size (≥ 10 cm; Table IV). The independent factors which influence the development of metastases on performing multivariate analysis were local recurrence, high histological grade and extracompartmental spread of the tumour (Table V).

Discussion

Adequate surgical excision remains the most important principle of treatment of patients with conventional chondrosarcoma. Radiotherapy and chemotherapy have been shown to play no significant role in the management of these patients.¹⁸⁻²³ Our study has focused on patients with localised conventional primary chondrosarcoma in an attempt to identify the factors which determine survival and local control.

Previous studies have included patients with several variants of chondrosarcoma as a group and have also included those with and without metastases at the time of diagnosis.^{10,24,25} The criteria for diagnosis of malignant cartilage tumours in many studies are ill-defined and some have included benign tumours with suspected malignant potential.¹² We recognise that distinguishing between benign and low-grade malignant cartilage tumours is difficult. Many ancillary means have been used to aid in the diagnosis, but unfortunately it often remains unclear.^{26,27} For this reason we have not included such borderline

benign tumours as cartilaginous lesions of unknown malignant potential in our series. We have elected to use the relatively less subjective 'cut-off' feature of the permeative growth of the tumour into adjacent host bone (i.e., lamellar bone) as the criterion for malignancy.

We have recently reported our experience with clear-cell chondrosarcoma²⁸ and we believe that it differs significantly from conventional chondrosarcoma. Dedifferentiated

Table II. Univariate analysis for factors associated with development of local recurrence

	Number with local recurrence (%)	p value
Margin		
Adequate (n = 70)	5 (7)	<0.0001
Inadequate (n = 83)	35 (42)	
Size (cm)		
<10 (n = 75)	13 (17)	0.008
>10 (n = 68)	26 (39)	
Site		
Limb (n = 101)	23 (23)	0.24
Axial (n = 52)	17 (32)	
Grade		
1 (n = 76)	16 (21)	0.17
2 (n = 62)	17 (27)	
3 (n = 15)	7 (47)	
Compartment		
Intracompartmental (n = 35)	6 (17)	0.19
Extracompartmental (n = 118)	34 (29)	
Type of surgery		
Amputation (n = 27)	6 (21)	0.8
Limb salvage (n = 126)	34 (27)	

Table III. Multivariate analysis for factors affecting survival

	Hazard ratio	95% confidence interval	p value
Local recurrence	3.4	1.6 to 7.1	0.002
Grade	4.7	2.1 to 10.4	0.0001
Compartment	5.1	1.5 to 29.2	0.02
Size	1.6	0.7 to 4.0	0.4
Margins	1.0	0.7 to 2.6	0.3

Table IV. Multivariate analysis for factors affecting the development of local recurrence

	Hazard ratio	95% confidence interval	p value
Margins	8.0	3.0 to 20.9	<0.0001
Size	2.0	1.0 to 4.0	0.04
Compartment	1.1	0.4 to 2.7	0.8
Site of tumour	1.0	0.6 to 2.1	0.7
Grade	1.7	0.9 to 3.3	0.1

Table V. Multivariate analysis for factors affecting the development of metastases

	Hazard ratio	95% confidence interval	p value
Local recurrence	3.2	1.5 to 6.6	0.001
Grade	4.4	2.2 to 9.0	<0.0001
Compartment	4.2	1.3 to 14.2	0.02
Margins	2.0	0.9 to 4.7	0.08
Size	1.0	0.6 to 2.0	0.8

chondrosarcoma, however, behaves like high-grade conventional chondrosarcoma,^{5,6,12} hence its inclusion in our study. We consider that patients with conventional chondrosarcoma should be treated as a separate group, and also that the recent improvement in imaging techniques, centralisation of treatment and improved surgical expertise are important factors to consider when analysing patients with chondrosarcoma.

An important finding in our study is that the development of a local recurrence is only relevant to survival if the patient has metastases when the diagnosis of local recurrence is made. In patients without metastases at the time of detection of local recurrence, further radical surgical treat-

ment produced a 64% cumulative rate of survival at five years after treatment of the local recurrence. By contrast, only 5% of those presenting with a local recurrence and metastases achieved long-term survival. This clearly indicates that aggressive treatment of local recurrences should be performed on those patients who do not have metastases when the local recurrence is diagnosed.

All patients with intracompartmental tumours have achieved long-term survival compared with 56% of those with extracompartmental tumours. The latter tend to have a higher histological grade and often shown to occur in patients who have had inadequate surgery. Multivariate analysis reveals that this is still an independent risk factor

Table VI. Major series over the last three decades reporting the treatment and outcome of patients with chondrosarcoma, by percentage except for the number of patients

	Number of patients	Limb salvage	Amputation	Adequate margins	Overall local recurrence rate	Local recurrence rate with		Low-grade tumours	Ten-year survival
						Adequate surgery	Inadequate surgery		
Evans et al ¹⁰	71	NS*	NS	NS	45	16	93	45	67
Sanerkin et al ²⁹	62	NS	NS	45	58	NS	NS	63	58
Pritchard et al ¹¹	280	52	48	NS	33	NS	NS	34	46
Gitelis et al ⁹	125	66	34	50	34	6	69	26	50
Ucla et al ³¹	178	75	25	60	21	15	31	20	62
Lee et al ¹²	227	99	1	76	24	25	44	38	NS
Present study	153	82	18	46	26	7	45	49	70

* not stated

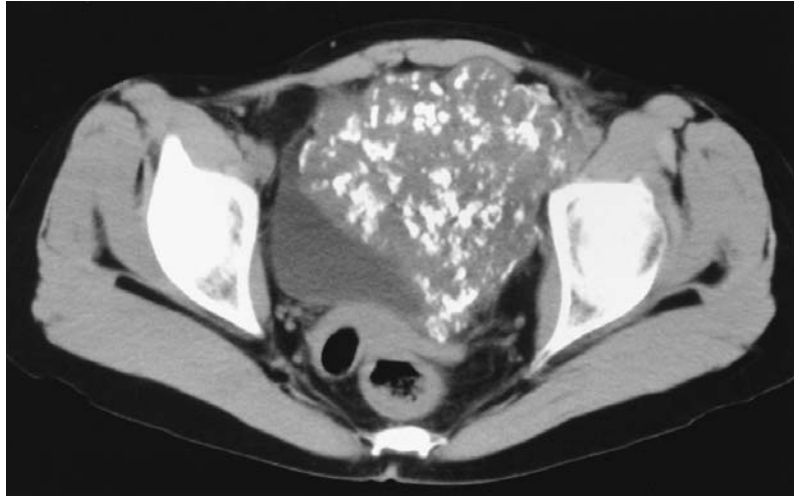


Fig. 5

CT scan of a patient with chondrosarcoma of the pelvis, illustrating the difficulty of achieving adequate margins in some patients.

for survival. The observation is not generally recognised or even reported in most series of chondrosarcomata. Björns-son et al¹³ noted that about 50% of chondrosarcomata in their series had extended into soft tissue, but did not examine this as a prognostic factor. Surprisingly, even high-grade intracompartmental tumours retained this good prognostic feature. This would suggest that an intra-compartmental tumour is biologically less aggressive than one which has extended into the soft tissue.

The rate of metastases in our series (32%) is similar to that in other studies.^{9,12,24} Patients with tumours larger than 10 cm in diameter and those with lesions located in the axial skeleton have been reported to be at high risk of distant spread and poor survival.^{10-12,24,29,30} Our results show that the significant risk factors for metastases include high histological grade, inadequate surgical margin, tumour size, extracompartmental spread of the lesion and the development of local recurrence on univariate analysis. Only high histological grade, extracompartmental spread and the development of local recurrence, however, are independent risk factors on multifactorial analysis. The size of the tumour and axial location are not independent risk factors for survival or the development of metastases in our series.

The definition of adequate margins varies in the different series. We consider that any margin which is less than 'wide' or 'radical' is inadequate for patients with chondrosarcoma, although we recognise that a wide margin may be impossible even with amputation in some patients (Fig. 5). It is possible that we have been more rigorous in our definition of the margins. Very often when a low-grade chondrosarcoma is resected the covering tissues will fall away at one stage of the operation leaving an exposed pseudocapsule of tumour. We would define this as a marginal excision, which we consider to be inadequate. This difference in definition is the explanation for the variation

in the rates of adequate margins in our series in contrast to some of the others shown in Table VI. This is supported by the fact that the rate of local recurrence in lesions with an adequate margin in our series is much lower than that in the others. Lee et al¹² reported a series of 227 patients of whom 99% had limb-preserving surgery and only 24% inadequate surgery. This compares with our rate of 54% with an inadequate margin. The overall local rate of recurrence in their series was similar to ours, but our rate of local recurrence in patients defined as having adequate surgery is 7% compared with 25% in their review (Table VI). All the groups reviewed in Table VI confirm the poorer results in patients who have had inadequate surgical margins.

Amputation and limb-preserving surgery result in similar rates of local control if adequate margins of excision are achieved. Most of the literature on chondrosarcoma has confirmed that inadequate surgical margins lead to a high risk of local recurrence which itself is a risk factor for survival. It has not been proved that limb-salvage surgery, with the risk of an inadequate margin, is justified when an alternative procedure, such as amputation, with a wide margin is possible. Multivariate analysis of our patients suggests that an operation with inadequate margins is associated with approximately eight times the risk of local recurrence than that with adequate margins. These patients with local recurrence are at three times the risk of both metastases and death. Decisions based on this information are difficult to make, particularly when the reported rates of survival, metastases and local recurrence are not significantly different in patients who have had amputation or limb-salvage surgery.

An overview of the main reported series from the last three decades (Table VI) suggests that with increasing rates of limb-salvage surgery, overall survival has remained unchanged. All the series clearly indicate, however, that

inadequate surgery increases the risk of local recurrence. We have not been able to show whether improvements in imaging combined with amputation, hopefully resulting in better surgical margins, will improve survival rates. Our data suggest that this may be the case, especially for patients with stage-IIB tumours.

Chondrosarcoma of bone is a surgically curable condition. Grading of the tumour by an experienced pathologist is essential. The surgeon's goal must be complete surgical excision of the tumour with a wide margin; anything less will jeopardise both local control of the disease and the chance of a cure.

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