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Original Paper

Prognostic Factors in Chordoma: Role of Postoperative Radiotherapy

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We have investigated prognostic factors for survival in a series of 26 patients with chordoma treated in Lyon, France, between 1979 and 1993. In this series, the median progression-free (PFS) and overall survival (OS) were 10 and 90 months, respectively. In univariate analysis, PFS, but not OS, was found significantly longer in males as compared to females (median: 19 versus 7 months, $P = 0.05$); and patients under 60 years of age had a longer PFS (median: 18 versus 6 months; $P = 0.06$) and OS (median: 108 versus 47+, $P = 0.05$) than older patients. A favourable prognostic subgroup including male patients under 60 years and a poor prognostic group including female patients and male over 60 years were thus defined (median PFS: 36 versus 6 months, $P = 0.001$; median OS: 108 versus 55+, $P = 0.15$). Primary treatment combining surgery and postoperative radiotherapy was associated with a longer PFS than surgery only (median: 36 versus 7 months, $P = 0.002$) in the whole series and in both prognostic subgroups.

Key words: chordoma, multivariate analysis, prognostic factors, radiotherapy surgery
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INTRODUCTION

CHORDOMA IS a rare neoplasm, accounting for 1% of malignant tumours, 5% of primary bone tumours and a third of spine tumours [1]. Chordomas arise from notochordal remnants along the midline of the neural axis and frequently involve the adjacent bones. Primary sites are most often the sacrococcyx (50%), the base of the skull (35%) and vertebrae (15%). Chordomas grow slowly and frequently present as large tumours at the initial diagnosis, in particular in the sacrococcygeal region. Complete surgery is generally considered as the standard treatment but cannot always be complete because of the proximity of the spinal cord, nerves, major vessels, optic chiasm and temporal lobes in the base of skull [2]. Futhermore, even after macroscopically complete surgery, local relapses are almost consistently observed [3, 4]. Radiotherapy alone or in combination with surgery is also generally unable to provide long-term local disease control. Thus, in most series, cure is infrequently achieved because of a high rate of local recurrence, and the optimal treatment remains to be defined [2]. Metastases are uncommon except for patients with massive tumours. Lymph nodes, lungs and skin are then frequently involved [3, 5, 6].

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Prognostic factors for survival or relapse in chordomas have been studied in a limited number of series [2, 6, 7, 8]. We analysed the role of prognostic factors and treatment in the outcome of a series of 26 chordomas treated in Lyon, France, between 1979 and 1993.

PATIENTS AND METHODS

Patients

The medical records of 26 patients with chordoma treated between 1979 and 1993 (median follow-up: 73 months) in two institutions (Centre Léon Bérard: $n = 20$ and Centre Hospitalier Lyon Sud: $n = 6$) were reviewed. There were 15 males and 11 females. The median age was 50 years (range: 22–73). Primary sites were the sacrococcygeal region ($n = 10$), the base of skull ($n = 8$), the cervical spine ($n = 4$), the lumbar spine ($n = 3$) and the dorsal spine ($n = 1$). 21 of the 26 patients had relapsed at least once (median number of relapses: 1, range: 0–9). 5 patients (19%) developed metastases during follow-up, at a median of 59 months after the diagnosis. The site of metastases were lymph nodes ($n = 2$), lung ($n = 2$), skin ($n = 2$) and bone ($n = 1$) (Table 1). Since this is a retrospective study, the frequency of follow-up examinations varied among patients, from once to three times a year. The endpoint for analysis was 1 February 1994.

Table 1. Description of the patients

UPN	Sex	Age	Tumour Site	First line treatment		Time to 1st local relapse (months)	Site(s) of distant relapses (months)	Last follow-up (months)	Status
				Complete resection	Radiotherapy (dose in Gy)				
B21	M	38	C	No	0	18		30	AWD
A31	F	31	C	No	0	4	Ly (59)	59	AWD
B23	M	40	C	Yes	20	102		108	UNK
A26	M	25	C	No	48	—		8	NED
B19	F	61	D	No	0	3		37	AWD
A35	M	63	L	No	0	2		27	DOD
A40	M	55	L	No	0	7	B (7)	36	AWD
A06	F	45	L	No	0	7		56	AWD
A89	M	41	S	No	0	19		36	AWD
A60	F	43	S	No	0	2		23	NED
A99	F	68	S	No	0	—		0	DOD
A35	M	61	S	No	0	6		8	PR
A42	M	45	S	No	30	22	Skin,Ly(52,54)	92	DOD
A63	M	60	S	No	30	—		9	NED
A00	M	48	S	No	30	61	Skin,L(81,90)	128	DOD
A70	M	53	S	No	36	—		2	NED
A57	F	44	S	Yes	56	18	L(44)	56	DOD
A51	M	57	S	No	64	9		58	AWD
B20	F	48	Sk	No	0	10		59	AWD
B22	F	58	Sk	No	0	6		40	AWD
B24	F	69	Sk	No	0	8		48	AWD
A25	F	22	Sk	No	0	60		130	UNK
A93	M	73	Sk	No	50	—		2	NED
A98	F	47	Sk	Yes	50	5		13	DOD
A52	M	43	Sk	No	50	37		53	DOD
A72	M	54	Sk	Yes	72	48		54	AWD

UPN, unique patient number; C, cervical; D, dorsal; L, lumbar; Sk, skull; S, sacrum; Ly, lymph nodes; B, bones; AWD, alive with disease; DOD, dead of disease; PR, partial remission; UNK, unknown status (evaluation not performed at the last follow-up); NED, no evidence of progressive disease.

Treatment

The primary treatment was only surgery in 14 patients and a combination of surgery and radiotherapy in 12 patients. Complete removal of the tumour was performed in 4 cases: sacrum (n = 1), cervical spine (n = 1), and base of the skull (n = 2) (Table 1). The remaining patients underwent a macroscopically incomplete removal of the tumour: in 17 patients with vertebral chordomas, laminectomy with incomplete removal of tumours in the extradural space and adjacent bone was performed. In 5 patients with tumour of the base of the skull, the surgery was incomplete because of the close proximity of critical anatomical structures. There was one operative death.

The dose of radiation after primary surgery was different for each type of primary site (Table 1). Tumours of the base of skull received 60 Gy (range: 50–72 Gy), given at 1.8–2.0 Gy per fraction, five fractions per week. For tumours of the upper lumbar, thoracic and cervical spine, the radiation dose was limited to 40–45 Gy (range: 20–48 Gy) with the same fractionation. For tumours of the lower lumbar and sacral segments, the dose to the central tumour was 64 Gy (range: 30–64 Gy). All patients were treated with cobalt or linac photon beams plus electron and 1 patient with proton plus electron beams for a chordoma of the base of skull. There were no late complications due to radiotherapy, in particular spinal cord or brain sequelae.

The treatment of the first relapse (n = 21) was only surgery in 4 patients, only radiotherapy in 5 patients (cobalt, photon, electron or proton beams with doses ranging from 24 to 65 Gy), surgery with postoperative radiotherapy for 5 patients, surgery and chemotherapy in 2 patients, and only chemotherapy for 2 patients. 3 patients received only symptomatic treatment. Of note, all 21 first relapses occurred at the primary site; a synchronous bone metastasis was diagnosed in 1 patient. The treatment of the second relapse (n = 8) was only surgery for 1 patient, only radiotherapy for 1 patient, surgery with postoperative radiotherapy for 3 patients, surgery and chemotherapy for 2 patients, and symptomatic treatment for 1 patient.

Chemotherapy was used to treat disseminated or recurrent disease in a small number of patients. Seven patients received chemotherapy: only ifosfamide (6 g/m^2) in 1 patient, the MAID regimen (mesna, 2500 mg/m^2/day days 1–4 + ifosfamide, 2500 mg/m^2/day days 1–3 + doxorubicin, 20 mg/m^2 + decarbazine, 300 mg/m^2) [9] in 3 patients, the HELP regimen (vindesine, 4 mg/m^2 day 1, ifosfamide, 3 g/m^2 days 1–2, cisplatin, 100 mg/m^2 day 3) [10] in 1 patient, the IVA regimen (ifosfamide, 3 g/m^2 + vincristine, 2 mg/m^2 + actinomycin D, 0.5 mg/m^2) in 1 patient, cyclophosphamide (500 mg/m^2/day days 1–7) + VP16 (500 mg/m^2) + epirubicin (50 mg/m^2) in 1 patient.

Statistics

Statistical analysis was performed using the procedures of the BMDP package. Survival was analysed according to the method of Kaplan and Meier [11]. Comparison of survival was performed

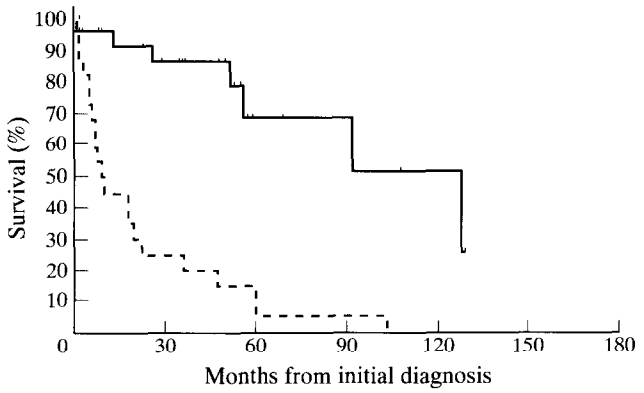

Figure 1. Progression-free (– – –) and overall (——) survival in the 26 patients with chordoma.

using the log rank test. Multivariate analysis was performed usng the Cox model [12]. In order to assess the impact of local radiotherapy after initial surgery, we evaluated the prognostic value of this parameter with the Cox model by running a model in which the two prognostic factors (age, sex) were blocked during the procedure.

RESULTS

In this series of 26 patients, the median progression-free survival (PFS) was 10 months and median overall survival (OS) was 90 months (Figure 1). The prognostic value of three parameters was investigated: sex, age and tumour site.

Progression-free survival was significantly longer in males as compared to females (Figure 2a, median: 19 versus 7 months, $P = 0.05$), whereas OS was not significant different in the two groups (Figure 2c). Patients under 60 years had a longer PFS (Figure 2b, median: 18 versus 6 months, $P = 0.06$) and OS (Figure 2d, median OS: 128 versus 47+ months, $P = 0.05$) as compared to older patients. Neither PFS nor OS were different among tumour sites. A multivariate analysis of prognostic factors including three parameters (1: age <60 years; 2: sex; 3: tumour localisation; sacrococcygeal versus others) was performed using the Cox model. Only age ≥60 years and female sex were found to have an independent prognostic value for PFS with relative risks of 2.61 and 2.85, respectively.

These results enable two prognostic groups for PFS to be distinguished. The favourable prognosis subgroup includes males aged under 60 years ($n = 12$, 46% of the series) whereas the poor prognostic subgroups include males aged over 60 years and female ($n = 14$; 54% of the series). The two prognostic groups have a significantly different PFS (Figure 3, median: 36 versus 6 months, $P = 0.001$). OS is also shorter in the poor prognostic group (median: 55+ versus 108 months for the favourable prognostic group), although the difference is not statistically significant ($P = 0.15$). Survival was analysed according to local treatment at the initial diagnosis: surgery alone versus surgery plus postoperative radiotherapy (Figure 4). PFS was significantly longer in patients treated with a combination of surgery and postoperative radiotherapy as compared to those treated with surgery only (Figure 4, median PFS: 36 versus 7 months, $P = 0.002$). OS was not significantly different in patients treated with surgery alone and surgery plus radiotherapy. Of note, PFS was not superior in patients in whom a complete removal of the tumour was achieved. The impact of the primary treatment was analysed in the two above defined prognostic groups. A longer PFS was observed in patients

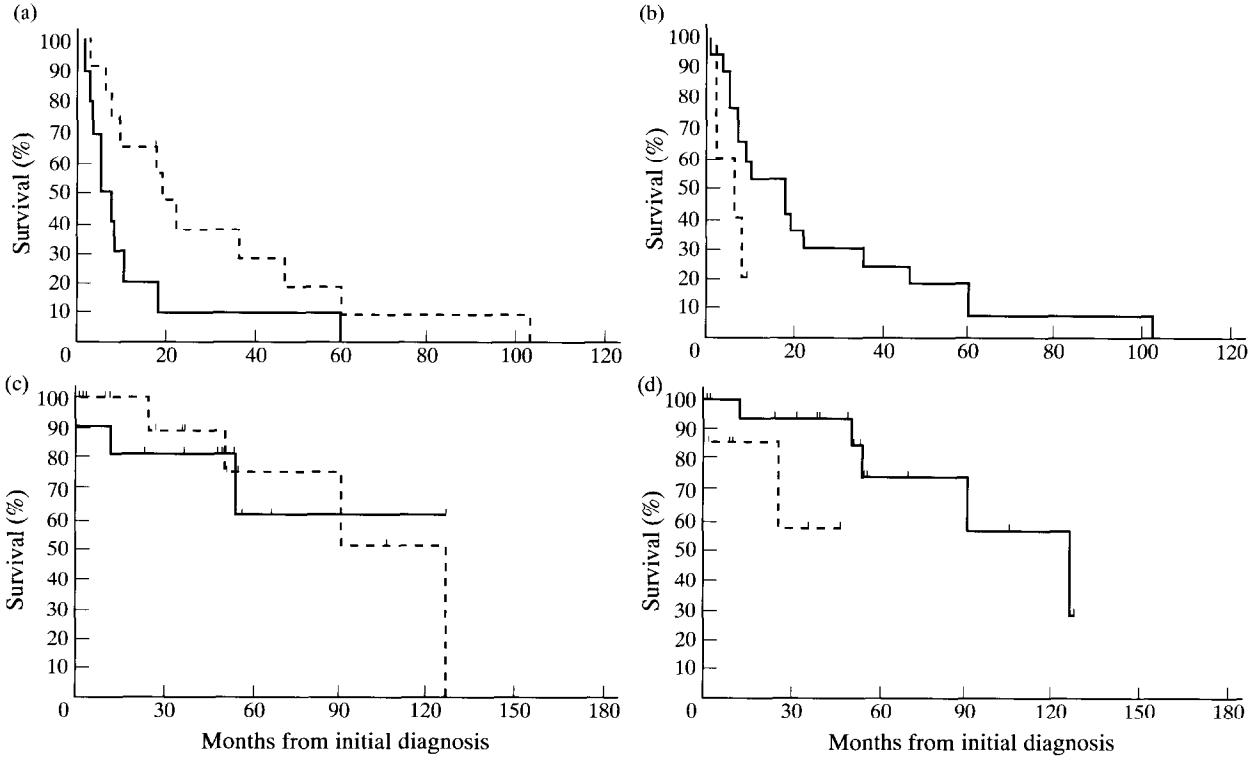

Figure 2. (a) Progression-free survival of male (– – –) and female (——) patients. (b) Progression-free survival of patients aged over (– – –) and under 60 years (——). (c) Overall survival of male (– – –) and female (——) patients. (d) Overall survival of patients aged over (– – –) and under 60 years (——).

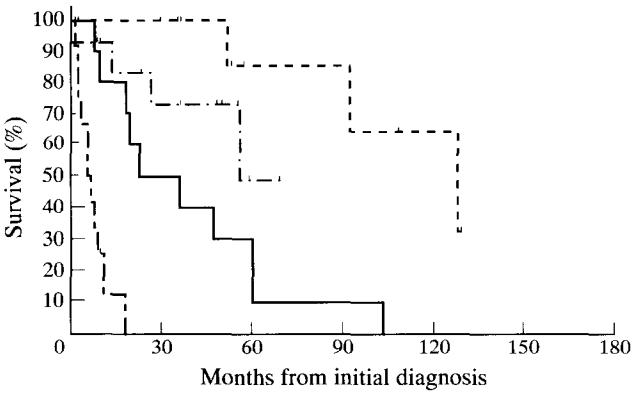

Figure 3. Progression-free survival of the favourable prognostic group, i.e. males <60 years (——) and the poor prognostic group, i.e. females and males ≥60 years (— – —). Overall survival of the favourable prognostic group, i.e. males <60 years (– – – –) and the poor prognostic group, i.e. females and males ≥60 years (— · —).

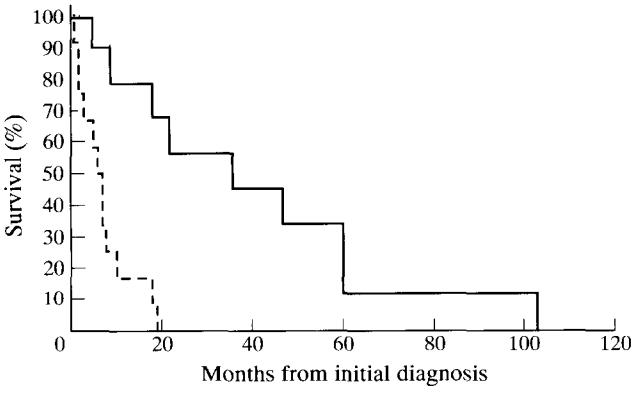

Figure 4. Progression-free survival of patients treated with surgery alone (– – –) and surgery plus radiotherapy (——).

treated with combination therapy (surgery and postoperative radiotherapy) in the favourable prognostic group ($P = 0.02$) as well as in the poor prognostic group ($P = 0.09$). 7 patients received chemotherapy for local or metastatic relapse. None achieved objective response to chemotherapy.

DISCUSSION

The objectives of this study were to analyse prognostic factors and determine the impact of treatment on survival in 26 patients with chordoma treated in Lyon between 1979 and 1993. Since chordoma is a rare tumour, the number of patients in this series as well as in most series of the literature is limited. The clinical characteristics of these patients were comparable to that of other series, in terms of age, sex and tumour sites [1, 5, 6, 8, 13].

Age and sex were identified as independent prognosic factors by univariate and multivariate analysis in this series. The age at the initial diagnosis (≤60 years versus >60 years) was inversely correlated to PFS and OS. The unfavourable outcome of female patients in terms of PFS has already been reported [7, 8], although inconsistently [6]. In contrast with a previous publication, OS was not significantly shorter in female patients in this series [8]. This could be related to the limited follow-up in this series as compared to the median survival of chordoma patients. The biological basis for the inverse correlation between sex and PFS remains unclear. High concentrations of receptors for sex steroid hormones, in particular progesterone and androgens, have been detected in chordoma [14]. This suggests that the growth of chordoma could be regulated by sex steroid hormones, in particular androgens or progesterone. In favour of the last hypothesis, PFS of postmenopausal female patients was comparable to that of men of the same age in our series (data not shown). These observations indicate a possible role for hormonal treatment in chordoma, in particular when one considers the very poor results achieved by chemotherapy for disseminated or locally advanced chordoma in this series as well as in other series [6, 15].

PFS or OS were not found to be significantly different for patients with different tumour sites in this series. This observation contrasts with previous reports in the literature showing longer overall survival of patients with sacrococcygeal localisation compared to others [1, 6, 15]. The reasons for this discrepancy are not clear and could be due to the limited number of patients in all chordoma series. It should be noted that the tumour site did not influence survival in univariate as well as in multivariate analysis in our series.

These results enable two prognostic subgroups with a discriminant PFS to be distinguished. The favourable prognostic group includes males aged under 60 years, whereas males over 60 years and females belong to the poor prognostic group. Of note, the median OS of males under 60 years was twice as long as the remaining patients.

In contrast with other studies [3, 4, 6, 8, 15], no significant differences of PFS or OS were observed between patients in whom complete removal of the tumour was achieved as compared to others. This could be due to the use of postoperative radiotherapy after partial removal, although it should be noted that all patients in whom complete removal was performed also received postoperative radiotherapy. In univariate analysis, a first line treatment combining maximal surgical resection followed by local radiotherapy yielded a significantly longer PFS as compared to surgery alone in this series. Although postoperative radiotherapy is generally recommended as adjuvant treatment following tumour removal [2, 5, 6, 16], its capacity to reduce local relapse rates remains controversial [2, 4, 6, 15]. The results presented here are in favour of combination treatment and are in agreement with several series in the literature [6, 15]. It is noteworthy that the improvement of PFS with combination treatment was confirmed by the multivariate analysis in which the two prognostic factors (age, sex) were blocked. No improvement of OS was observed with combination therapy in our series in agreement with other reports [2, 9].

Although treatment with radiotherapy was associated with prolongation of PFS, local relapses occurred in the majority of patients of this series as well as in most reports. This suggests that radiotherapy is capable of delaying relapses but not of improving the cure rate in these patients. Of note, no correlation between the dose of radiation and the incidence of relapse was observed in our series.

Chemotherapy was ineffective in the 7 patients of this series. None of the patients receiving chemotherapy experienced an objective response. In particular, ifosfamide in combination with doxorubicin and dacarbazine was found ineffective in our experience, in contrast with a recently published report on dedifferentiated chordoma [17]. These results are consistent with previous reports showing poor efficacy of chemotherapy in chordoma: several chemotherapeutic agents have been tested without sucess: vinblastine; methotrexate, actinomycin D,

epoxypiperazine, cyclophosphamide and 5-fluorouracil. Chordoma remains a poorly chemosensitive tumour which requires novel inventive therapeutic procedures [6, 15]. Hormonal treatment could represent an alternative therapeutic modality which should be evaluated in prospective trials.

In conclusion, these results indicate that age and sex are independent prognostic factors in chordoma. The combination of surgery and radiotherapy in first line treatment was associated with a longer PFS, but the projected 10 years disease-free survival is 0 in this series.

1. Touboul E, Khelif A, Guerin RA. Les tumeurs primitives durachis. Aspect oncologique inital: épidémiologie, classification anatomo-prognostique et thérapeuticque. *Neurochirurgie* 1989, **35**, 312–316.
2. Keisch ME, Garcia DM, Shibuya RB. Retrospective long-term follow-up analysis in 21 patients with chordomas of various sites treated at a single institution. *J Neurosurg* 1991, **75**, 374–377.
3. Malawer MM, Link MP, Donaldson SS. Sarcoma of bone. In De Vita VT, Hellman S, Rosenberg SA. *Cancer Principles and Practices of Oncology*, 4th Edition. Philadelphia, J.B. Lippincott, 1993, 1559–1560.
4. Kaiser TE, Pritchard DJ, Vuni KK. Clinocopathologic study of sacrococcygeal chordoma. *Cancer* 1984, **54**, 2574–2578.
5. Rich TA, Schiller A, Suit HD, Mankin HJ. Clinical and pathologic review of 48 cases of chordoma. *Cancer* 1985, **56**, 182–187.
6. Sundaresan N, Galicich JH, Chu FCH, Huvos AG. Spinal chordomas. *J Neurosurg* 1979, **50**, 312–319.
7. Austin-Seymour M, Munzenrider J, Goitein M, *et al.* Fractionated proton radiation therapy of chordoma and low-grade chondrosarcoma of the base of the skull. *J Neurosurg* 1989, **70**, 13–17.
8. Bjornsson J, Wold LE, Ebersold MJ, Laws ER. Chordoma of the mobile spine: a clinicopathologic analysis of 40 patients. *Cancer* 1993, **71**, 735–740.
9. Elias A, Ryan L, Sulkes A, Collins J, Aisner J, Antman KH. Response to mesna, doxorubicin, ifosfamide and dacarbazine in 108 patients with metastatic or unresectable sarcoma and no prior chemotherapy. *J Clin Oncol* 1989, **7**, 1208–1216.
10. Biron P, Blay JY, Belouineau F, Philip T, Brunat-Mentigny M. Pilot study of the HELP regimen in adult osteosarcoma. *Proc Am Soc Clin Oncol* 1993, **471**.
11. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958, **53**, 457–81.
12. Cox DR. Regression models and life tables. *JR Stat Soc [B]* 1972, **34**, 187–220.
13. Cummings BJ, Hodson I, Bush RS. Chordoma: the result of megavoltage radiation therapy. *Int J Radiat Oncol Biol Phys* 1983, **9**, 633–642.
14. Stojkovic RR, Jovancevic M, Santel DJ, Grcevic N, Gamulin S. Sex steroid receptors in intracranial tumors. *Cancer* 1990, **65**, 1968–1970.
15. Touboul E, Khelif A, Guérin RA. Tumeurs primitives du rachis: radiothérapie et chimiothérapie. *Neurochirurgie* 1989, **35**, 342–350.
16. Saxton JP. Chordoma. *Int J Radiat Oncol Biol Phys* 1981, **7**, 913–915.
17. Fleming GF, Heimann PS, Stephens JK, *et al.* Dedifferentiated chordoma. Response to agressive chemotherapy in two cases. *Cancer* 1993, **72**, 714–718.

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