Acta Oncologica Vol. 31, No. 8, pp. 847-851, 1992

CHORDOMA-NATURAL HISTORY, TREATMENT AND PROGNOSIS

The Florence Radiotherapy Department experience (1956-1990) and a critical review of the literature

STEFANO M. MAGRINI, MARIA G. PAPI, FRANCO MARLETTA, SALVATORE TOMASELLI, ENRICO CELLAI, VALIANO MUNGAI and GIANPAOLO BITI

Fifteen cases of chordoma, seen between 1956 and 1990 at the Florence Radiotherapy Department are reported. Twelve of them were treated with radiotherapy and surgery, while one was left untreated. We analyzed the course of the disease in the treated cases, with particular emphasis on the problem of symptom control. The natural history of the disease seemed to be only marginally affected by the treatment and new therapeutic options are strongly needed. While actuarial survival rates at 5 and 10 years were 58% and 35% respectively (owing to the slow growth rate of this neoplasm), 10 years' symptomatic progression-free, symptom-free, and disease-free survival rates were only 25%, 17% and 8% respectively.

Chordoma is a rare tumor that represents between 1 and 4% of malignant bone tumors and about 20% of those arising from the axial skeleton in large hospital series. It originates from remnants of an embryonic structure, the notochord, and arises usually from the sacrum (about 50%), the clivus (35%) or the 'true' vertebrae above sacrum (15%) (1). More than 1 000 cases have been published to date. Surgery, radiotherapy or a combination of both do not seem to substantially modify the natural history of the disease. Patients with chordomas often live for many years, even if they very seldom have been rendered tumor-free by the treatment. Death is most often caused by consequences of uncontrolled local tumor growth. Distant metastases may occur, but the frequency varies largely between the published series. However, metastatic disease is rarely directly or indirectly responsible for death (2). We reviewed the Florence Radiotherapy Department experience of chordoma and the literature on this subject in an attempt to elucidate the role of the various treatment modalities. The therapeutic results have been evaluated both in terms of symptomatic relief and in terms of local control and survival. Particular emphasis has been put on the problem of symptom control.

Received 1 April 1992.
Accepted 11 September 1992.
From Department of Radiotherapy, (S. M. Magrini, M. G. Papi, E. Cellai, V. Mungai, G. Biti) Florence, Italy; Department of Radiotherapy (F. Marletta, S. Tomaselli), Catania, Italy.
Correspondence to: Dr Stefano Maria Magrini, U.O. Radioterapia U.S.L. 10/D, Policlinico di Careggi, Viale Morgagni 85, I-50134 Florence, Italy.

Material and Methods

We reviewed the files of patients treated at our institution between 1955 and 1990, and were able to identify 15 cases originally diagnosed as 'chordoma'. Histological verification was available for all but two patients and was always confirmed by our pathology department when the original histologic examination had been performed elsewhere. One of the patients without histological diagnosis was subsequently discovered to have a myeloma and was excluded. The clinical information available for the other patient was judged as sufficient to warrant inclusion in the analysis. The clinical records of another patient (treated in 1959) were largely incomplete, and this patient was there-

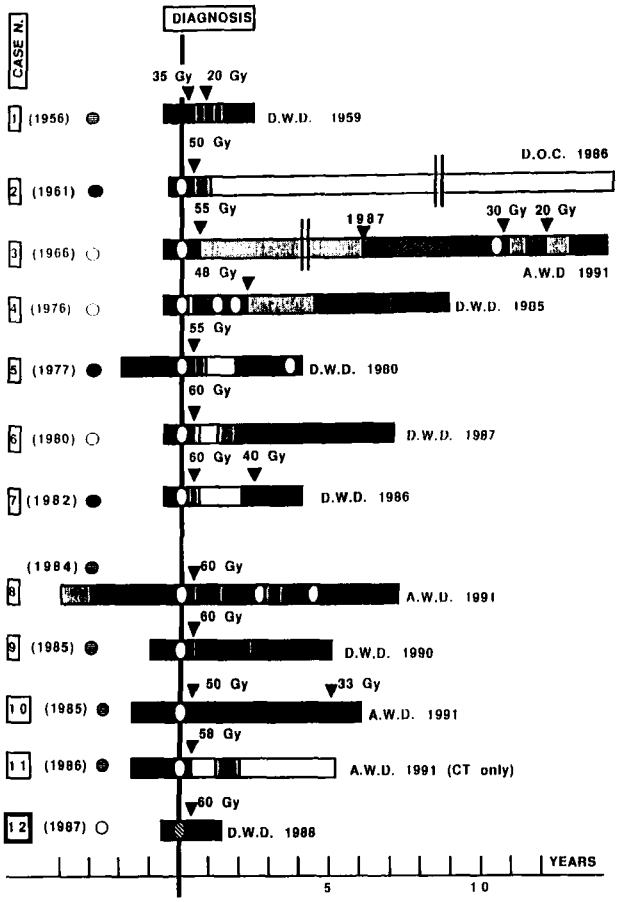

Fig. 1. The clinical course of the disease in the 12 treated patients. (19...) date of diagnosis. ●: sacrum. ●: clivus. ○: 'true' vertebrae. ◉: biopsy. ○: partial resection. ■: symptomatic. ▨: partially symptomatic. ▥: slightly symptomatic. □: asymptomatic. D.O.C.: dead other cause. D.W.D.: dead with disease. A.W.D.: alive with disease.

fore excluded from the analysis. Our material thus consisted of 13 patients (7 males and 6 females). The youngest patient was 15 yeas old at diagnosis and the oldest 82 years (mean age: 54 years). Four tumors were situated in clivus, 6 in sacrum, and 3 in 'true' vertebrae.

The duration and evolution of symptoms, the extension of the primary tumor and the presence of lymph node or distant metastases was recorded in an attempt to define the clinical courses (Fig. 1). Patients were classified as slightly, partially or fully symptomatic according to an arbitrary scale, considering both the severity and the nature of the symptom(s)—pain, neurological deficits, etc.

Twelve of the patients were treated with radiotherapy, after incomplete resection of the primary tumor in 10 patients and after biopsy only in one of them. One patient was left untreated after biopsy of a mass in nasopharynx. This patient (a 72-year-old male) had a huge intracranial tumor and was regarded as beyond the possibility of reasonable palliation by radiotherapy.

In some cases, after primary treatment, a second course of radiotherapy was given, or the patient was again submitted to surgery, sometimes more than once, because of progressive or relapsing disease (Fig. 1). In none of the patients operated on due to relapse was complete macroscopic resection achieved.

Radiotherapy was given with conventional fractionation (2 Gy × 5/week) in 10/12 treated cases; one patient was given 3 Gy fractions three times a week, and the remaining one 4 Gy twice a week. All cases but one were treated with high energy photon or electron beams. One patient was treated with orthovoltage x-rays. The doses and treatment courses are shown in Fig. 1.

A major problem arises when endpoints for survival curves have to be chosen. The overall disease-specific survival curve does not adequately mirror the treatment results, due to the long natural history of the disease. We thus calculated not only the actuarial (Kaplan Meier) disease-specific survival but also actuarial symptomatic progression-free survival, symptom-free survival and disease-free survival. Worsening of symptoms, presence of symptoms and presence of measurable disease respectively represent unfavorable outcomes in the last mentioned three types of analysis.

The possible relationship between total tumor dose and therapeutic result was tentatively explored by relating the dose to the length of the time elapsed before progression of symptoms.

Results

Natural history. Large local tumor masses were present at diagnosis in many patients, probably due to the slow gradual evolution of symptoms (Fig. 1). There was no obvious difference in the extent of the disease between the early and late periods of patient admittance. All tumors cases arising from 'true' vertebrae involved at least three vertebrae. In 3 of the 6 patients with sacral presentation, the tendency of the neoplasm to grow anteriorly was manifested by the presence of large soft tissue masses. In two cases of sacral chordoma soft tissue extensions into the gluteal region were present and in one of them the gluteal mass attained a maximum diameter of over 20 cm during the follow-up. In all patients with cranial lesions the tumor volume exceeded 20 cm^3. The cavernous sinus was invaded in two of them and the anterior pole of the temporal lobe in one. In one patient a huge intracranial mass was present. This patient was left untreated, and died 45 months after the beginning of symptoms. This patient was the only one in our series who developed lymph node metastases and in none of the patients were distant metastases observed on admission or during follow-up.

Treatment results. The survival pattern of the 12 treated patients is shown in Fig. 2. Actuarial 5-year disease-spe-

cific survival rate (OS) was 58% (SE 14%); corresponding rates for symptomatic progression-free (PFS), symptom-free (SFS), and disease-free (DFS) survival were 25% (SE 13), 17% (SE 11) and 8% (SE 8) respectively. The 10-year rate for OS was 35% while the corresponding rates for PFS, SFS and DFS were similar to the calculated 5-year rates. Among the 5-year survivors, only about one-third were symptom-free and only about 15% disease-free.

Primary treatment. Surgery alone was used in only one patient, and produced complete but transient symptomatic control (case 4, Fig. 1). Radiotherapy alone produced transient, partial symptomatic benefit in one of the two patients to whom it was given; no symptomatic effect was obtained in the other patient (cases 1 and 12, Fig. 1). As to combined modality treatment, incomplete surgery by itself provided partial symptomatic control in 3/9 patients; subsequent radiotherapy produced complete symptomatic relief in 5/9 patients and partial benefit in 3/9.

Re-treatments. Four patients were surgically retreated with a total of 6 operations. Low-dose radiotherapy was added after two of these operations. Surgery provided symptomatic relief by itself in two occasions; the combination of low-dose irradiation and surgery was of benefit on the two occasions when it was used. Radiotherapy alone was used on four occasions in four other patients and was of symptomatic benefit in two of them. As a rule, however, symptomatic relief was only temporary. Moreover, retreatment was not always effective and sometimes even dangerous. The symptoms thus worsened obviously in two patients with clivus lesions (cases 5 and 7, Fig. 1); the first one was submitted to surgery for relapse about three years after initial surgery, which was followed by postoperative radiotherapy (55 Gy); the second one was, after incomplete resection, retreated elsewhere with radiotherapy (40 Gy) towards volumes partially overlapping those treated at our institution (60 Gy).

Dose-effect relationship. The possible relationship between the total radiation dose in the tumor and symptomatic control was also explored. Every radiotherapy course (no matter if given as primary treatment or for relapse/progression) was considered separately. A clear-cut dose-effect relationship was not evident, even if all patients who became free from symptomatic progression for more than two years after radiotherapy had received doses above 50 Gy.

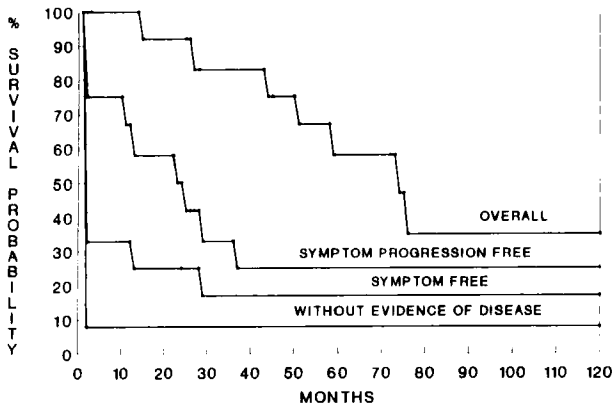

Fig. 2. Overall disease-specific, symptomatic progression-free, symptom-free, and disease-free survival for the 12 treated patients.

Discussion

Natural history. The well-known heterogeneity of chordomas as to their evolution was apparent also in our series. A relatively indolent course is the predominant pattern, even for intracranial lesions, as illustrated by the only patient in our series who was left untreated. Another patient (case 3, Fig. 1) is living with disease 25 years after diagnosis. The often slow, gradual evolution of symptoms certainly explains the presence of large tumor masses at diagnosis. However, a more aggressive course may occur as in cases 1 and 12 in our material (Fig. 1).

Treatment options. A summary of more than half of the published cases is shown in the Table. Reports which include less than 10 cases or lack relevant information are not listed in the Table. The patterns of natural history and survival in our series were quite similar to those reported in the literature.

The therapeutic attitude has remained largely unchanged during the last 50 years. The patients are as a rule first submitted to surgery, in an attempt to remove all the macroscopic disease. This is, however, very rarely possible and radiotherapy is then often used in a hope to sterilize or at least to inhibit the growth of the residual tumor. High total doses are often used, owing to the known radioresistance of chordoma. Unfortunately, the therapeutic results have remained invariable poor over the years. It is not surprising, therefore, that in some more recent papers the possibility of more aggressive surgery and/or radiotherapy has been discussed.

Surgery. Several authors have discussed the possibility of more aggressive surgery (1, 19, 20). In our series radical resection was never achieved. This might have been a result of unfavorable selection of patients referred for radiotherapy, but may also indicate that early diagnosis, even in the last decade, is rare. An estimate of the probability of obtaining radical removal can be derived from the literature (Table) and suggests that radical surgery is possible only in 10–20% of the cases.

Radiotherapy. The debate in the radiotherapeutic literature has focused on the optimal total dose. Several authors (3, 4, 6, 7, 9–11) underline the need for very high total doses (at the level 60 Gy or more). Considerable experience (18, 21) has been accumulated concerning treatment of clivus chordomas with heavy particles or protons. However, there is a preponderance of smaller tumors in these series since small treatment volumes are needed for the use of these techniques. A paper published in 1988 by the San Francisco group (18), for example, showed that the 5-year

Table

Summary of data from the most relevant published series

Ref. no.	No. of cases	Site of disease % C	S	V	Completely resected %	Postop. radiotherapy %	Radiotherapy alone	5-Year survival %	5-Year disease control %	Mean radiation dose (Gy)
1	34	6	59	35	NS	NS	NS	40	NS	NS
2	54	–	67	33	17	66	14	60	8[2]	NS
3	25	52	36	12	4	60	40	44	33[3]	54
4	18	17	78	5	11	55	22	NS	31[3]	52
5	21	52	14	34	0	29	52	50	5[2]	60
6	48	29	40	31	21	35	31	45	10[2]	8 < 45 (4) 14 46–60 12 > 60
7	10	50	40	10	0	40	40	88	44[2]	48
8	25	40	48	12	4	40	44	62	46[3]	47
9	14	21	64	15	57	7	36	43	21[2]	40
10	19	31	58	11	21	42	31	44	17[2]	56
11	15	33	47	20	7	27	53	43	7[2]	>60
12–13	155[5]	36	49	15	NS	34	24	35	21[2]	NS
14	33[6]	9	82	9	30	21	12	40	25[2]	NS
15	21	24	62	14	43	38	19	74	NS	NS
16	18	61	33	6	0	67	0	38	NS	NS
17	25[7]	28	52	20	NS	11	0	13	5[2]	NS
18	25	100	0	0	0	100	0	50	55[3]	70[8]

Abbreviations: C = clivus; S = sacrum; V = 'true' vertebrae

1) Radiotherapy alone means radiotherapy given after biopsy.
2) Survival without evidence of disease.
3) Survival without symptomatic progression.
4) Number of patients in each dose group.
5), 6), 7) Treatment and survival data only available for 83/155, 27/33 and 19/25 patients respectively.
8) Doses expressed as CGE (Cobalt Gray Equivalent); disease control rate refers in this series to local control.

local control rate for smaller tumors ($<20\ cm^3$) was more than two times higher than that for larger tumors (80% vs 33%). Other authors have expressed radically diverging opinions. One example is the Princess Margaret Hospital treatment philosophy. recently summarized by Cummings et al. (8). They advocate the use of short radiotherapy courses with lower total doses, judged sufficient for symptomatic relief, and repeated if symptomatic progression occurs. From published results they also derive the opinion that even high total doses (55–65 Gy) produce unsatisfactory long-term results. In our series, high radiation doses produced durable symptomatic results only in a few cases. It should be noticed, however that lower doses never achieved long-lasting palliation and that the only two patients who survived symptom-free for more than 5 years had been treated with doses in excess of 50 Gy.

Cummings et al. (8) claim that multiple daily fractionation might be a promising technique. However, their opinion is based on 4 cases only and to our knowledge the more recent literature has not confirmed an advantage of this technique. Other radiotherapeutic modalities as treatment with neutron beams or radioactive implants, preoperative irradiation, or irradiation associated with hyperbaric oxygen have been used sporadically, so far without obvious advantage.

Retreatments and chemotherapy. Patients with relapsing or progressing disease are often submitted to repeated surgical and radiotherapeutical procedures. This practice may produce some symptomatic benefit. However, it may sometimes be dangerous and the symptomatic effect is often of short duration, certainly due to the fact that relapses mainly occur in areas previously involved by the neoplasm.

A few chemotherapeutic regimens have been tested in patients with chordoma, mainly for relapsing disease, without appreciable benefit (2, 14). At present chemotherapy has no proven place in the treatment of chordoma (16, 22).

In conclusion, no great advances have been made during the last few years in the treatment of chordomas possibly with the exception of the rare, very small clivus chordomas that can be treated by highly specialized, stereotactic, small-volume, 'radiosurgical' techniques. For the majority of chordomas it seems likely that surgical excision (as complete as technically feasible) followed by irradiation with a high (but not excessively high) dose will continue for some time to be the treatment of choice due to the fact

that more effective alternatives are lacking. In our opinion the main therapeutic goal should be the achievement of maximal symptom relief. The often excruciating course of this disease is characterized by long periods of suffering, caused by neurological symptoms and/or pain. Therefore, particular attention should be devoted to pain control and to prevention of complications from the neurologic deficits.

ACKNOWLEDGEMENTS

This work was partly supported by a grant from the Italian National Research Council (CNR, Grant n.92.02488.CT04). We are indebted to Mrs. Chiara Castellini Massaini for the revision of the English translation of the text.

REFERENCES

1. Sundaresan N, Rosenthal DI, Schiller A, Krol G. Chordomas. In: Sundaresan N, Schmidek HH, Schiller AL, Rosenthal D, eds. Tumors of the spine, Philadelphia: W.B. Saunders, 1990: 192-213.
2. Sundaresan N, Galicich JH, Chu FCH, Huvos AG. Spinal chordomas. J Neurosurg 1979; 50: 312-9.
3. Fuller DB, Bloom JG. Radiotherapy for chordoma. Int J Radiat Oncol Biol Phys 1988; 15: 331-9.
4. Lybeert MLM, Meerwaldt JH. Chordoma—Report on treatment results in eighteen cases. Acta Radiol Oncol 1986; 25: 41-3.
5. Amendola BE, Amendola MA, Oliver E, McClatchey KD. Chordoma: role of radiation therapy. Radiology 1986; 158: 839-43.
6. Rich TA, Schiller A, Suit HD, Mankin HJ. Clinical and pathologic review of 48 cases of chordoma. Cancer 1985; 56: 182-7.
7. Reddy EK, Mansfield CM, Hartman GV. Chordoma. Int J Radiat Oncol Biol Phys 1981; 7: 1709-11.
8. Cummings BJ, Hodson I, Bush RS. Chordoma: the results of megavoltage radiation therapy. Int J Radiat Oncol Biol Phys 1983; 9: 633-42.
9. Tewfik HH, McGinnis WL, Nordstrom DG, Latourette HB. Chordoma. Evaluation of clinical behavior and treatment modalities. Int J Radiat Oncol Biol Phys 1977; 2: 959-62.
10. Saxton JP. Chordoma. Int J Radiat Oncol Biol Phys 1981; 7: 913-5.
11. Pearlman AW, Friedman M. Radical radiation therapy of chordoma. AJR Rad Ther Nucl Med 1970; 108: 333-41.
12. Heffelfinger MJ, Dahlin DC, MacCarthy CS, Beabout JW. Chordomas and cartilaginous tumors at the skull base. Cancer 1973; 32: 410-20.
13. Dahlin DC, MacCarty CS. Chordoma. A study of fifty-nine cases. Cancer 1952; 5: 1170-8.
14. Azzarelli A, Quagliuolo V, Cerasoli S, et al. Chordoma: Natural history and treatment results in 33 cases. J Surg Oncol 1988; 37: 185-91.
15. 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: 374-77.
16. Chetty R, Levin CV, Kalan MR. Chordoma: A 20-year clinicopathologic review of the experience at Groote Schuur Hospital. Cape Town. J Surg Oncol 1991; 46: 261-4.
17. Volpe R, Mazabraud A. A clinicopathologic review of 25 cases of chordoma. Am J Surg Pathol 1983; 7: 161-70.
18. Berson AM, Castro JR, Petti P, et al. Charged particle irradiation of chordoma and chondrosarcoma of the base of skull and cervical spine: the Lawrence Berkeley Laboratory experience. Int J Radiat Oncol Biol Phys 1988; 15: 559-65.
19. Nath Sen C, Sekhar L. The subtemporal and preauricolar infratemporal approach to intradural structures ventral to the brain stem. J Neurosurg 1990; 73: 345-54.
20. Uttley D, Moore A, Archer DJ. Surgical management of midline skull-base tumors: a new approach. J Neurosurg 1989; 71: 705-10.
21. Austin-Seymour M, Urie M, Munzenrider J, et al. Considerations in fractionated proton radiation therapy: clinical potentials and results. Radiother Oncol 1990; 17: 29-35.
22. Cummings BJ, Esses S, Harwood AR. The treatment of chordomas. Cancer Treat Rev 1982; 9: 299-311.