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OUTCOMES

Sacral Chordoma: Long-term Outcome of a Large Series of Patients Surgically Treated at Two Reference Centers

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Study Design. Retrospective case series.

Objective. To report on the natural history and long-term outcome of a large series of consecutive primary sacral chordoma patients surgically treated at two reference centers.

Summary of Background Data. Sacral chordomas are rare tumors with poor long-term prognosis mainly caused by local failure. Till date, a few large series with long follow up are available in literature.

Methods. All consecutive patients affected by primary localized sacral chordoma operated on at two Italian reference centers between 1981 and 2012 were included. Overall survival (OS), disease free survival (DFS), crude cumulative incidence (CCI) of local recurrence (LR), and distant metastases (DM) were calculated. Multivariable analyses for OS, DFS, LR, and DM were performed.

Results. A total of 99 patients were identified: 65 males and 34 females. Median age was 59 years (range 22–77 yrs), median tumor size was 9 cm (range 4–22). Nineteen patients received pre- or postoperative radiotherapy (RT). Wide (R0) surgical margins were achieved in 46 patients, marginal (R1) margins in 43 patients and intralesional (R2) margins in 10 patients. At a median follow up of 8.7 years (range 1–23.8 yrs) 30 patients died of disease, 31 patients developed local relapse, 16 patients developed distant metastasis, whereas 51 patients are alive without disease. OS and DFS at 5, 10, and 15 year were 92% and 63%, 45% and 62%, 36% and 21%, respectively, without any evidence of a plateau in the curves.CCI of LR and DM were 30% and 9% at 5 years, 46% and 18% at 10 years, 56% and 23% at 15 years. Size of the tumor and quality of surgical margins were the only significant predictors of long-term outcome. DFS for 15 years was, in fact, 49% for R0 and 7% for R1, respectively.

Conclusion. In this series, long-term outcome of resected sacral chordoma was poor, with less than 25% patients were disease-free at 15 years. Interestingly, only half of the patients treated with R0 resection had no evidence of recurrence at 15 years. When surgical margins are expected to be positive other treatment modalities should be considered, especially when expected sequelae are substantial as in the case of more cephalad levels of resection.

Key words: chemotherapy, chordoma, hadron radiation therapy, imatinib, prognostic factors: recurrence, metastasis, survival, sacrectomy, sacrum, surgery.

Level of Evidence: 3

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Chordoma is an extremely rare spine tumor with an expected incidence of less than one new case/1,000,000 inhabitants per year.[1] Although chordomas may arise at any site along the spine, the sacrum is the commonest location (50–60%) and has peculiar characteristics as tumors can grow to considerable size and involve the sacral nerves.[2–6] Surgery has been so far the cornerstone of treatment but local failure is common even years after primary surgery and postsurgical sequelae can be substantial.[7–11] In the recent years, there has been a growing interest

on the possible role of heavy particles radiation therapy (RT) as a definitive treatment to control the disease at a lesser cost for the patient, but no prospectively comparative studies are available so far.[12–18]

Indeed, we also lack retrospective case series analyses with a long follow up, providing reliable data on the natural history of the disease and suitable to serve as external controls for future prospective studies on new treatment strategies. In 2010, we published a retrospective analysis of two series of consecutive patients with chordoma of mobile spine and sacrum treated at two Italian main reference centers for this rare disease on a 28-year span—that is, from 1980 to 2008.[19] Now, we singled out patients with sacral chordoma presenting with primary untreated disease extending the series to those treated up to 2012 and providing a longer follow up.

MATERIALS AND METHODS

All consecutive patients affected by primary and localized sacral chordoma, surgically treated at Istituto Ortopedico Rizzoli (IOR), Bologna, and Fondazione IRCCS Istituto Nazionale dei Tumori (INT), Milano, between June 1981 and July 2012 were included. Clinical data were extracted from the two institutional prospective surgical databases. Data retrieved included: sex, date of biopsy, age at diagnosis, tumor site, tumor size, centers of primary tumor surgery (IOR, INT), tumor rupture (yes/no), chordoma subtype (conventional, chondroid, and dedifferentiated), brachyury expression, margin status, neoadjuvant/adjuvant radiotherapy (yes/no, dose in Gray), neoadjuvant/adjuvant chemotherapy (yes/no, regimen), dates and site of neoplastic events, and date of death or last follow-up.

We also recorded site and extension (local/metastatic) of recurrences, treatment (surgery/radiotherapy/chemotherapy/best supportive treatment), type of surgery (macroscopically complete/incomplete), and dates and site of further neoplastic events. In all cases, diagnosis was confirmed by at least two expert pathologists. Margins were inked and separately sampled and classified as negative (R0), positive (R1), or intralesional (R2).

From formalin-fixed paraffin-embedded material nuclear immunoreactivity for brachyury was tested in all 99 patients.

Before surgery, all patients underwent staging with chest x-ray or computed tomography (CT) scan.

This retrospective study was approved by the Ethic Committees of the two institutions.

Statistical Analysis

Primary endpoints of this retrospective cohort study were as follows:

- Overall survival (OS) is defined as the time from surgery to the date of death from any cause. Subjects alive at the time of the analysis were censored at the date of last contact.
- Disease free survival (DFS) is defined as the time from surgery to the date of local disease relapse, distant disease relapse, second primary malignancy, or death from any cause, whichever occurred first.
- Local recurrence (LR) is defined as the time from surgery to the date of local disease relapse. Distant relapse, second primary malignancy, or death before local disease relapse were considered competing events; subjects alive and not relapsed at the time of the analysis were censored at the last disease assessment date.
- Distant metastases (DM) are defined for each patient as the time from surgery to the date of distant disease relapse. Local relapse, second primary malignancy, or death before any distant disease relapse were considered competing events; subjects alive and not relapsed at the time of the analysis were censored at the last disease assessment date.

Secondary endpoint of this retrospective cohort study was postprogression survival (PPS), which is defined as the time from local disease relapse, distant disease relapse, or second primary malignancy, whichever occurred first, to the date of death from any cause. PPS was equal to 0 in case of death before disease relapse.

The Kaplan-Meier method was used to estimate survival function in absence of competing risks; the crude cumulative incidence (CCI) of local recurrence (CCI of LR) and distant metastasis (CCI of DM) was non parametrically estimated in presence of competing risks. The semiparametric Cox model and the Fine and Gray subdistribution hazards model were respectively used to estimate hazard ratio (HR) in absence and presence of competing risks.

The restricted mean at 10 years was considered an unbiased estimator of the PPS endpoint; the point estimate was calculated as the difference between OS restricted mean at 10 years and DFS restricted mean at 10 years. A bootstrap confidence interval (CI) was calculated: 500 bootstrap estimates of the PPS restricted mean at 10 years were calculated; these bootstrap estimates were ordered from low to high and the 13th value as the lower limit and the 488th value as the upper limit were taken.

Covariates analyzed as predictors of prognosis were: age, size (<9.5 cm/≥ 9.5 cm), site (S_1-S_2/S_3-coccyx), margins (R2/R1/R0), tumor rupture (yes/no), and radiotherapy(yes/no).

Baseline covariate distributions were summarized using descriptive statistics (median and range for continuous variables, and absolute and percentage frequencies for categorical variables).

Because of the descriptive nature of this study, hypothesis testing was applied qualitatively and not formally (*e.g.*, no threshold for statistical significance level was defined).

Statistical analysis was performed using SAS software (SAS Institute, Cary, NC), version 9.2; the statistical software R version 3.2.0 was used to perform the survival analysis in presence of competing risks. The R function ''cuminc'' and ''crr'' available in the ''cmprsk'' package

TABLE 1. Demographic and Clinic Characteristics of the Study Population

Patients	N°	%	IQR
Male	65	66	
Female	34	34	
Median Age (yrs)	59		49–64
Median tumor size (cm)	9		7–13
Level of lesion			
S1-S2	57	58	
S3-coccyx	42	42	
Surgical margins			
R0	46	47	
R1	43	43	
R2	10	10	
Chemotherapy			
Done	3	3	
Not Done	96	97	
Radiation therapy			
Done	17	17	
Not done	82	83	

IQR indicates interquartile range; R0, wide resection; R1, marginal resection; R2, intralesional resection; S1, first sacral vertebra; S2, second sacral vertebra; S3, third sacral vertebra.

were used respectively to estimate the CCI and the HR parameter. Stata software, version 12.1 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP) was used to estimate the PPS restricted mean at 10 years.

RESULTS

Patients

A total of 99 patients were identified. Median follow up was 8.7 years (range 1–23.8 yrs). Main characteristics of the study population are listed in Table 1. Ninety-seven patients had conventional chordoma, one patient had the chondroid subtype, and one patient the dedifferentiated variant. Male sex was prevalent (66%). Median age at the time of presentation was 60 years [interquartile range (IQR) 49–64 yrs], median tumor size 9 cm (IQR 7–13). Chordoma arose from S1-S2 in 59 patients whereas in 40 patients it was localized at S3 or below.

Overall, surgical margins at the histological analysis were negative (R0) in 46 patients, positive (R1) in 43 patients, and intralesional (R2) in 10 patients. Intraoperative tumor rupture occurred in 14 patients.

Radiation therapy (RT) was delivered in two patients presenting with bulky disease in neoadjuvant setting and in 17 patients after R1/R2 surgery. No chemotherapy was given preoperatively whereas nine patients received medical treatment in the advanced phase, for unresectable local recurrence or metastatic disease.

Primary Tumor

Thirty-three (33%) deaths were recorded with 30 (91%) of them directly related to chordoma. Among them, 20% patients died of metastatic disease without any evidence of local recurrence, 37% patients died of local recurrence without evidence of metastases, whereas 43% patients died presenting both local and distant relapse. Till date, 15 patients are alive with disease and 51 patients are alive without disease (nine of them after being treated for local or distant relapses).

Overall, 5, 10, and 15-year OS was 92% (95% CI: 85–96%), 63% (95% CI: 49–75%), and 45% (95% CI: 30–59%), respectively, with a median OS of 13.3 years (Table 2, Figure 1A).

On multivariable analysis (Table 3), tumor size and surgical margins were the only significant prognostic factors

TABLE 2. Rate for 5-Years, 10-Years, and 15-Years of OS, DFS, CCI of LR, and DM

Endpoint	Median	5-Yrs	10-Yrs	15-Yrs
DFS	6.9 (95% CI: 5.2–8.9)	62% (95% CI: 51–71%)	36% (95% CI: 25–48%)	21% (95% CI: 11–35%)
CCI-LR	14.0 (95% CI: 7.4–not defined)	30% (95% CI: 21–40%)	46% (95% CI: 35–57%)	56% (95% CI: 41–68%)
CCI-DM	not defined	9% (95% CI: 5–16%)	18% (95% CI: 10–27%)	23% (95% CI: 13–35%)
OS	13.3 (95%CI: 10.0–21.7)	92% (95% CI: 85–96%)	63% (95% CI: 49–75%)	45% (95% CI: 30–59%)

CCI indicates crude cumulative incidence; CI, confidence interval; DFS, disease free survival; DM, distant metastases; LR, local recurrence; OS, overall survival.

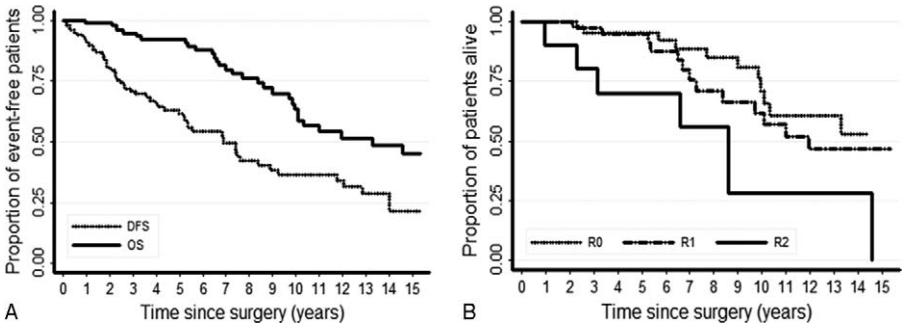

Figure 1. (**A**) Overall survival and disease free survival of the whole series of patients. (**B**) Overall survival of the whole series of patients according to resection margins.

for OS. Overall, 5, 10, and 15-year OS was 95% (95% CI: 83–99%), 71% (95% CI: 49–85%), and 53% (95% CI: 29–72%) and 95% (95% CI: 81–99%), 62% (95% CI: 39–78%), and 47% (95% CI: 26–66%) in case of R0 and R1 margins, respectively (Table 4, Figure 1B). A trend towards a worse outcome was observed also for tumors arising from S1-S2 compared with tumors arising from S3 and below. Administration of RT did not significantly affect OS, but only four patients received at least 60 Gy and none received >70 Gy.

Moreover, 47 patients (48%) developed local or distant relapses as first event. In our study, 5, 10, and 15-year DFS was 62% (95% CI: 51–71%), 36% (95% CI: 25–48%), and 21% (95% CI: 11–35%), respectively, with a median DFS of 6.9 years (Table 2, Figure 1 A). On multivariable analysis, tumor size and surgical margins were the only significant prognostic factors for DFS. Overall, 5, 10, and 15-year DFS was 78% (95% CI: 61–88%), 56% (95% CI: 37–72%), and 49% (95% CI: 28–67%) and 52% (95% CI: 35–67%), 22% (95% CI: 9–38%), and 7% (95% CI: 1–21%) in case of R0 and R1 margins, respectively (Table 4, Figure 2 A). A trend towards a worse outcome was observed also for tumors arising from S1-S2 compared with tumors arising from S3 and below.

Total 38 patients (38%) experienced locoregional recurrences. In 31 patients, LR was the first event, whereas in three patients LR and DM were concomitant and in four patients local relapse occurred after distant metastases. Thus, 5, 10, and 15-year CCI of LR after surgery of primary tumor were 30% (95% CI: 21–40%), 46% (95% CI: 35–57%), and 57% (95% CI: 41–68%), respectively (Table 2, Figure 2 B). On multivariable analysis, tumor size and surgical margins were the only prognostic factors for LR. Thus, 5, 10, and 15-year CCI of LR was 18% (95% CI: 5–30%), 31% (95% CI: 15–47%), and 31% (95% CI: 15–47%) and 38% (95% CI: 22–54%), 58% (95% CI: 39–76%), and 70% (95% CI: 52–88%) in case of R0 and R1 margins, respectively. A trend towards a worse outcome was observed also for tumors arising from S1-S2 compared with tumors arising from S3 and below. Administration of RT did not significantly affect the incidence of LR, but only four patients received at least 60 Gy, and none > 70Gy.

Total 28 patients (28%) developed distant metastases, located to lungs (16 patients), bone (five patients), and soft tissues (four patients). One patient had brain and lymph node metastases and one patient metastasized to multiple sites. DM occurred as a first event in 13 patients and concomitant to LR in three patients. The 5, 10, and 15-year CCI of DM after surgery of primary tumor was 9% (95% CI: 5–16%), 18% (95% CI: 10–27%), and 24% (95% CI: 13–35%), respectively (Table 2, Figure 2 B). On multivariable analysis, a trend towards a worse outcome was observed for larger tumor and inadequate resection margins.

Postprogression Survival (PPS)

A total of 47 (48%) patients relapsed; 31 patients recurred locally first, three patients presented concomitant local and distant relapse, whereas 13 patients developed only distant metastases. Median follow-up was 5 years. Among 38 patients who experienced local failure overall, 15, 7, and 8 patients were operated on with R0, R1, and R2 surgical margins, respectively. Eight patients were found unresectable, two of them underwent RT and six patients received only palliative treatment. A 5-years OS after local and distant relapse were 57% (95% CI: 37–73%) and 32% (95% CI: 8–59%), respectively (Figure 3). Median postdistant metastases OS was 4.7 years. On multivariable analysis age < 60 years and size of the primary tumor < 9.5 cm showed a favorable trend whereas status of resection margins did not influence the postprogression outcome.

DISCUSSION

In this series of 99 consecutive patients affected by primary sacral chordoma treated with surgery over a 30-years time span at two reference sarcoma centers, median OS and DFS were 13.3 and 6.9 years, respectively. Quality of surgical margins was the most significant prognosticator for DFS, with 49% patients resected with R0 margins and only 7% of those resected with R1 being continuously disease-free at 15 years. The corresponding median DFS was 12 *versus* 5.2 years, respectively. Tumor size also impacted OS and DFS. Approximately, one fourth of patients developed distant metastasis on the long run, most often to the lungs, this figure being possibly underestimated because of the retrospective nature of this series.

Although all limitations of retrospective analyses should obviously be discounted, we report on a large series of consecutive patients exclusively with sacral, previously untreated chordoma, providing a 10-year median follow-up. Data on postrelapse outcome are included. In very rare

TABLE 3. Hazard Ratio Estimates With 95% Confidence Intervals and *P* From the Univariable and Multivariable Cox Proportional Hazard Models on Overall, Local Relapse-free, and Distant Relapse-free Survival

	Univariable Analysis			
Variable	**Endpoint**	**HR**	**95% CI**	***P***
Age at surgery (Continuous)	DFS	0.92	0.73–1.16	0.474
	CCI LR	0.80	0.62–1.03	0.088
	CCI DM	1.15	0.75–1.75	0.531
	OS	0.91	0.66–1.24	0.544
Sex (Denominator: Female)	DFS	1.06	0.61–1.84	0.828
	CCI LR	0.79	0.43–1.45	0.442
	CCI DM	1.93	0.64–5.86	0.245
	OS	1.42	0.69–2.91	0.343
Tumor size (Denominator: < 9.5cm)	DFS	1.12	1.06–1.19	<0.001
	CCI LR	1.08	1.01–1.17	0.026
	CCI DM	1.10	0.99–1.21	0.073
	OS	1.10	1.02–1.19	0.010
Site (Denominator: S1-S2)	DFS	0.84	0.46–1.52	0.567
	CCI LR	0.73	0.36–1.47	0.373
	CCI DM	1.17	0.42–3.27	0.771
	OS	0.93	0.41–2.10	0.857
Surgical margins (Denominator: R0)* Test per trend	DFS	R1: 2.72 R2: 5.39	R1: 1.48–4.98 R2: 2.24–12.97	<0.001*
	CCI LR	R1: 2.60 R2: 3.60	R1: 1.28–5.27 R2: 1.29–10.02	0.003
	CCI DM	R1: 1.47 R2: 4.90	R1: 0.47–4.58 R2: 1.32–18.22	0.051
	OS	R1: 1.17 R2: 3.61	R1: 0.55–2.50 R2: 1.35–9.68	0.048*
Radiation therapy (Denominator: No)	DFS	1.34	0.69–2.60	0.391
	CCI LR	0.97	0.46–2.05	0.935
	CCI DM	1.17	0.33–4.19	0.810
	OS	1.51	0.68–3.39	0.315
Multivariable analysis				
Tumor size (Denominator: < 9.5cm)	DFS	1.13	1.06–1.21	<0.001
	CCI LR	1.07	0.99–1.16	0.095
	CCI DM	1.09	0.98–1.21	0.120
	OS	1.11	1.03–1.20	0.008
Surgical margins (Denominator: R0)* Test per trend	DFS	R1: 2.31 R2: 6.24	R1: 1.22–4.36 R2: 2.51–15.49	<0.001*
	CCI LR	R1: 2.13 R2: 3.44	R1: 1.02–4.44 R2: 1.20–9.87	0.011
	CCI DM	R1: 1.41 R2: 3.99	R1: 0.46–4.29 R2: 1.08–14.81	0.077
	OS	R1: 0.90 R2: 3.43	R1: 0.40–1.99 R2: 1.26–9.33	0.114*

CCI indicates crude cumulative incidence; CI, confidence interval; DFS, disease free survival; DM, distant metastases; HR, hazard ratio; LR, local recurrence; OS, overall survival; R0, wide resection; R1, marginal resection; R2, intralesional resection; S1, first sacral vertebra; S2, second sacral vertebra; S3, third sacral vertebra.

cancers, retrospective series may well be the only opportunity to understand the natural history of the disease. This applies to chordoma, a very rare cancer with an incidence in the range of one per million each year. The importance of a long follow-up in chordoma is clear from available studies, as they have a high tendency to recur even after many years from initial surgery with < 25% patients alive and free of disease at 15 years. Table 5 enlists the main published series of chordoma patients.[8,13–17,19,20–27] Interestingly, relapse-free survival curves do not reach a plateau even at

TABLE 4. Surgical Margins and Outcome				
Endpoint	**Median**	**5-Years**	**10-Years**	**15-Years**
		R0		
DFS	12.0 (95% CI: 6.9–21.7)	78% (95% CI: 61–88%)	56% (95% CI: 37–72%)	49% (95% CI: 28–67%)
OS	17.8 (95% CI: 10.0–21.7)	95% (95% CI: 83–99%)	71% (95% CI: 49–85%)	53% (95% CI: 29–72%)
		R1		
DFS	5.2 (95% CI: 2.5–7.4)	52% (95% CI: 35–67%)	22% (95% CI: 9–38%)	7% (95% CI: 1–21%)
OS	11.9 (95% CI: 7.3–non defined)	95% (95% CI: 81–99%)	62% (95% CI: 39–78%)	47% (95% CI: 26–66%)
		R2		
DFS	2.2 (95% CI: 0.1–5.2)	30% (95% CI: 7–58%)	not defined	not defined
OS	8.6 (95%CI: 1.0–14.6)	70% (95% CI: 33–89%)	28% (95% CI: 2–68%)	0% (95% CI: 0–non defined)

CI indicates confidence interval; DFS, disease free survival; OS, overall survival; R0, wide resection; R1, marginal resection; R2, intralesional resection.

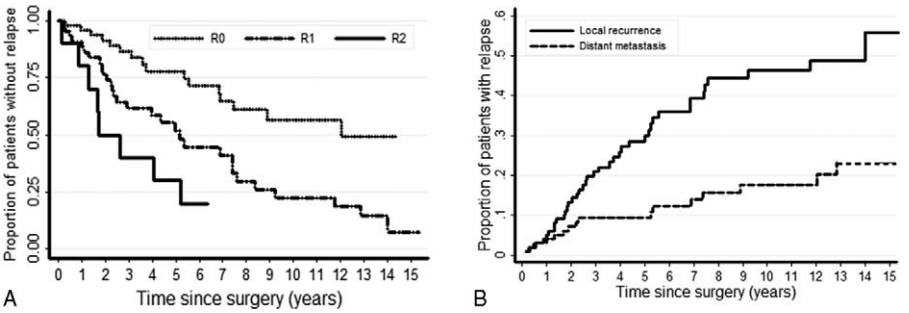

Figure 2. (**A**) Disease-free survival of the whole series of patients according to resection margins. (**B**) Crude cumulative incidence of local recurrence and distant metastases of the whole series of patients.

the 15-year time point. Moreover, the overall survival curve does not reach a plateau at 15 years, as patients experiencing local or distant recurrences may live with their disease for long, though eventually dying of it. In this series, the 15-year disease-free rate is below 25%, being higher than 50% at 5 years. This stresses the importance of analyzing data on a long follow up when evaluating the efficacy of new treatment modalities. This is a major challenge, especially when technologies evolve rapidly and would deserve to be immediately assessed, in a disease with such a low cure rate.

With regard to prognostic factors, quality of surgical margins was crucial. One half of patients who could be treated with a R0 resection had no evidence of recurrence at 15 years *versus* 7% in the presence of R1 margins. In addition, in spite of attempting to achieve negative margins in all cases, this was feasible only in less than half of them. Furthermore, the achievement of negative margins often required extended resections, resulting in significant morbidities in relation to the level of sacral amputation. Although our retrospective analysis could not provide details about quality of life, it is well known that the sacrifice of S2 nerve roots translates into a urinary/fecal dysfunction and sexual disorders, and walking ability is affected if S1 roots are involved.[28–32] This means that currently surgery can be proposed to patients when R0 margins can be expected, knowing that more proximal resections entail a major price to pay in terms of quality of life. When only a R1 margin is achieved, chances of a long-term local control of disease are very low. We confirm that local control is the main prognostic issue, because in our series 80% of patients dying of chordoma did so with a local relapse in place. Unfortunately, the role of nonsurgical options is still undefined, particularly with regard to heavy particles RT. Till date, only a few series with long follow up are available and

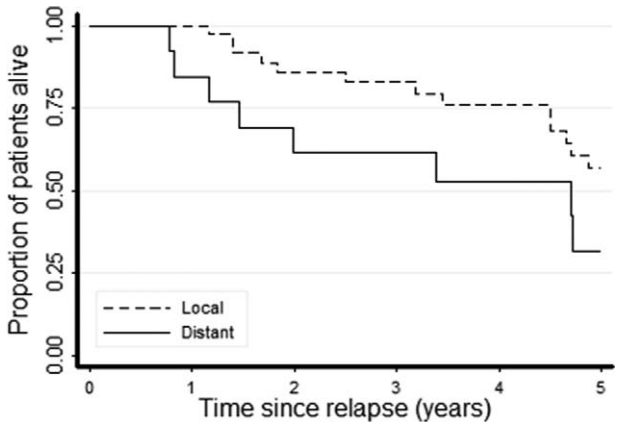

Figure 3. Post local and distant relapse overall survival.

TABLE 5. Largest Published Series Reporting Sacral Chordoma

Series	Number of Patients	Treatment	Median FU (Yrs)	Survival Rate	Local Progression	Distant Metastasis
Bergh *et al*[8]	39*	Surgery ± pre/postoperative photons	8.1	52% at 20 years	40% overall†	30% overall†
Baratti *et al*[9]	56‡	Surgery ± postoperative photons	5.9	49% at 10 years	24% of DFS at 10 years	
Fuchs *et al* [20]	53	Surgery ± postoperative photons	7.8	52% at 10 years	54% at 10 years	NR
Schwab *et al* [21]	42	Surgery ± postoperative photons	NR	35% at 10 years	40% overall	31% overall
Zabel Du-Bois *et al* [22]	34	IMRT ± prior surgery	4.5	70% at 5 years	77% at 5 years	9% at 5 years
Ruggieri *et al* [23]	56	Surgery	9.5	71% at 10 years	48% at 10 years	30% overall
Stacchiotti *et al* [19]	138§	Surgery ± postoperative photons	11.8	54% at 10 years	77% at 5 years	28% at 10 years
Chen et al. [24]	36	Surgery ± postoperative photons	6.2	59% at 10 years	NR	NR
Imai *et al* [13]	95	Carbon ions	3.5	86% at 5 years	12% at 5 years	NR
Nishida *et al* [14]	17	Surgery (10)/carbons (7)	4.7	74% at 5 years	23% at 5 years	NR
Mima *et al* [15]	23	Carbon ions/protons	3.2	83% at 3 years	6% at 3 years	23% at 3 years
Chen *et al* [16]	24¶	Protons/photons	4.7	78% at 5 years	20% at 5 years	23% at 5 years
DeLaney *et al* [17]	50‖	Photons/protons ± prior surgery	7.3	65% at 8 years	15% at 8 years (8% at 8 years)**	NR
Dubory *et al* [25]	29	Surgery ± postoperative photons	6.5	84% at 10 years	46% at 10 years	NR
Varga *et al* [26]	167	Surgery ± postoperative photons/protons	3.2	40% at 10 years	75% at 10 years	NR
Xie *et al* [27]	54	Surgery	7.8	45% at 15 years	80% at 15 years	NR
Our Study	99	Surgery ± pre/postoperative photons	8.7	45% at 15 years	56% at 15 years	23% at 15 years

*9 patients with mobile spine chordoma.
†considering only sacral chordoma.
‡6 patients with mobile spine chordoma.
§30 patients with mobile spine chordoma.
¶5 patients with mobile spine chordoma.
‖21 patients with mobile spine chordoma.
**23 patients with mobile spine chordoma.
DFS indicates disease free survival; IMRT, intensity-modulated radiotherapy; NR, not reported.

no comparative studies have been carried out.[12–18] A recent position article on sacral chordoma left this issue open, considering both treatments as valid approaches to be discussed with the patients, although still recognizing surgery as the mainstay of treatment.[11] We are launching a prospective international comparative trial on surgery *versus* radiation therapy in sacral chordomas.

On the other hand, 20% of chordoma deaths in this series were related to metastatic disease and 43% involved both local and distant disease. Overall, 28% of our patients showed metastatic disease during their follow up. These figures are consistent with a metastatic potential for this disease which is higher than generally believed. This stresses the importance of staging and follow-up investigations incorporating chest and abdominal assessments.[33–35] Of course, it stresses the importance to develop new medical therapies in this disease. In 2004, we reported the activity of imatinib in advanced chordoma,[36] and some studies have then been undertaken on molecularly targeted agents, although the efficacy of available medical treatments is still confined to the palliative setting.[37–39]

With regard to postrelapse local treatments, in our series achieving R0 margins on local recurrences did not improve postrelapse survival. Once again this shows how local control of the primary tumor is currently the only crucial factor for patient's chances of cure.[27,40] Thus, the best approach to local failures is still debatable. We are setting up a consensus process among chordoma experts about treatment of local relapses, though in the lack of convincing evidence.

In conclusion, *en-bloc* sacrectomy with negative margins still represents the cornerstone of treatment for sacral chordoma but it is challenging and feasible only in a minority of cases. This is especially clear if follow up is prolonged. Distant metastasis does exist in chordoma, contrary to

earlier beliefs. Both new local regional and systemic treatments are needed in this disease. Retrospective analyses such as the one we provided herein may be useful as historical controls for prospective studies on such new treatments, in a rare disease wherein controlled evidence is so difficult to generate.

Key Points

- Retrospective analysis of 99 consecutive patients, surgically treated over 30 years time span at two Italian referral centers, affected by primary and localized sacral chordoma.
- A total of 30 patients died of disease, whereas local recurrence and distant metastasis occurred as first event in 31 and 16 patients, respectively.
- In our study, 10-years OS and DFS were 63% and 36%, respectively. Ten-years crude cumulative incidence of LR and DM were 46% and 18%, respectively.
- On multivariable analysis, size of the tumor and quality of surgical margins were the only significant predictors of long-term outcome.
- Moreover, 5-years OS after local and distant relapse were 57% and 32%, respectively.

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