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Clinical Study

Sacral chordoma: a clinical review of 101 cases with 30-year experience in a single institution

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Abstract

BACKGROUND: Local recurrence rates are high in sacral chordoma patients. Adjuvant radiotherapy may play a role in increasing local control. Patients with locally recurrent tumors continue to comprise a significant proportion of the sacral chordoma population and appear to have worse prognosis than those with primary tumors. High-quality studies comparing presentation and treatments for primary and first local recurrent sacral chordoma tumors are sparse.

PURPOSE: To determine: whether there is a difference in how primary and tumors at first recurrence present; the overall survival, local relapse-free survival, and distant relapse-free survival rates and prognostic factors for patients presenting with a primary tumor; overall survival, local relapse-free survival, and distant relapse-free survival rates and prognostic factors for patients presenting with a first local relapse; if there any differences in overall survival, local relapse-free survival, and distant relapse-free survival rates between patients presenting with a primary tumor and those with a first local relapse.

STUDY DESIGN: Retrospective case series.

PATIENT SAMPLE: One hundred one sacral chordoma cases.

OUTCOME MEASURE: Overall survival, local relapse-free survival, and distant relapse-free survival rates.

METHODS: Between 1978 and 2013, 131 patients with sacral chordoma were seen. Of them, 17 patients (13%) presented with a history of more than one local recurrence. One patient (1%) presented with multiple distant metastases. Ten patients (8%) had less than 36 months of follow-up and had no event (eg, death, local recurrence, or distant metastasis). A total of 102 patients met our inclusion criteria: patients with primary or first recurrent tumors, without metastatic disease, who underwent surgery and with at least 36 months of follow-up. One patient (1%) died intraoperatively; therefore, 101 patients were included in the present analysis. Cox proportional hazards regression analysis was performed for primary and local recurrent tumor separately and to compare primary and local recurrent tumors.

RESULTS: We analyzed 73 primary and 28 first time recurrent sacral chordomas. Tumor size at presentation was different for primary and recurrent tumors (primary median size: 158 cm^3, interquartile range [IQR]: 46–634; recurrent median size: 39 cm^3, IQR: 14–175; p=.001). Overall

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survival at 5 and 10 years for the primary tumors was 79% and 59%, respectively. Local relapse-free survival at 5 years was 86%. For primary tumors, not receiving radiation was an independent predictor for worse local relapse-free survival (hazard ratio [HR]: 0.20; 95% confidence interval [CI]: 0.0043–0.90; p=.004) and increased tumor size was an independent predictor for both worse overall survival (HR: 1.68; 95% CI: 1.38–2.42; p=.004) and worse distant relapse-free survival (HR: 2.25; 95% CI: 1.47–3.44; p<.001). For recurrent tumors, the 5- and 10-year overall survival was 65% and 40%, respectively. Local relapse-free survival at 5 years was 79% for recurrent tumors. On bivariate analysis, increased tumor size was a significant predictor for worse survival (LR median: 338 mL; IQR: 218–503 mL; no LR median: 26 mL; IQR: 9–71 mL). A trend was seen toward better distant relapse survival for tumors presenting as a primary tumor (HR: 0.51; 95% CI: 0.25–1.06; p=.072).

CONCLUSION: Using a combination of surgical resection and adjuvant radiotherapy allowed us to obtain a good overall survival, local relapse-free survival, and distant relapse-free survival in patients presenting with either a primary tumor or with a first time local recurrent tumor.

Keywords: Chordoma; Local recurrent; Primary; Radiotherapy; Sacrum; Survival.

Introduction

Chordoma is a rare malignant tumor with an incidence of 0.1 cases per 100,000 per year and is mostly seen in the sacrum [34]. The tumors tend to be large at presentation and surgical resection is often required. The balance between adequate resection and sparing of surrounding vital structures makes local control difficult. Local recurrence rates are relatively high, ranging from 43% to 85% [1–5,13,14,16–20,22,24,26–28,31–33,35,40,41], and its minimal response to chemotherapy and low-dose radiotherapy make adjuvant treatments less attractive [36]. Advancements in the delivery of radiation have made it safe to deliver high dosages of radiation. Therefore, radiation is gaining popularity as an adjuvant treatment and is also being studied as a primary treatment [7,10,12]. Even though, local control is the main challenge in sacral chordoma and therefore the population with locally recurrent tumor is relatively high, especially in tertiary referral centers [2,4,14,22,32,33,35,40].

To our knowledge, there are no studies comparing presentation and treatments for primary and first local recurrent sacral chordoma tumors within a single institution or through a meta-analysis. In a previous series, a total of 71 sacral chordomas were analyzed, of these 60 were primary and 11 had a previous intralesion resection [2]. Results were given for both groups combined, not separately. The same goes for Ruggieri et al. [32], where oncological results reported for 56 sacral chordomas of which 9 underwent previous intralesional resection. Several other studies also analyzed both groups as a whole [3,4,13,14,28,33,35]. Analyzing these groups together is only appropriate if they are similar in terms of presentation and treatment, which we hypothesize is not the case.

Therefore, we asked the following questions: Are there differences in characteristics of primary and local recurrent chordomas?; What are the overall survival (OS), local relapse-free survival (L-RFS), and distant relapse-free survival (D-RFS) rates prognostic factors for patients presenting with a primary tumor; What are the OS, L-RFS, and D-RFS rates and prognostic factors for patients presenting with a first local relapse?; Are there any differences in OS, L-RFS, and D-RFS rates between patients presenting with a primary tumor and patients presenting with a first local relapse?

Methods

After approval from our institutional review board, a retrospective review was conducted of all sacral chordoma patients that were operated on in our tertiary care center between 1978 and 2013. We included patients with primary or first recurrent tumors, without metastatic disease, who underwent surgery with at least 36 months of follow-up. Seventy-six patients did not undergo surgery because of an unresectable tumor, chose to get treatment elsewhere, or received definitive radiotherapy. We identified 131 patients in our orthopedic oncology database. Of them, 17 patients (13%) presented with a history of more than one local recurrence. One patient (1%) presented with multiple distant metastases. Ten patients (8%) had less than 36 months of follow-up and had no event (death, local recurrence, or distant metastasis). A total of 102 patients met our inclusion criteria. One patient (1%) died intraoperatively; therefore, 101 patients were considered for the present analysis. Seven fellowship-trained orthopedic oncology surgeons performed all surgeries of whom one surgeon performed more than 50% of the surgeries.

Clinical data were extracted from the database and medical records. For all patients, data at presentation were collected, including sex, date of diagnosis, tumor location, tumor size, and tumor histology. Per our routine, all patients undergo a staging computed tomography (CT) scan or a chest x-ray prior to surgery. For patients who presented with a first local recurrence at our institution, data on

previous treatment (date of initial diagnosis, surgery: yes/no, positive margins: yes/no, radiation: yes/no) were also collected. Treatment data included age at treatment, preoperative radiotherapy (yes/no, dose in Gray [Gy]), surgical management (single-staged or two-staged procedure), level of resection (above or below S3), intraoperative radiotherapy (yes/no, dose [Gy]), lumbo-pelvic reconstruction (yes/no), ileo- or colostomy (yes/no), surgical margin status (negative [R0] or positive [R1 or R2[39]]), postoperative radiotherapy (yes/no, dose [Gy]), and chemotherapy (yes/no). Negative margins were defined as the absence of tumor in the resection margins in the pathology examination of the en bloc resected specimen. Positive margins were defined as the presence of any tumor (microscopically or gross) in the surgical margins on pathology examination of the resected specimen. The decision for an illeostomy or colostomy was based on the level of the nerve root resection and patient preference. Lumbosacral reconstruction was routinely done in patients who underwent an osteotomy higher than at the S2–S3 level and received high-dose radiation. Reconstruction was also done in patients with an osteotomy above the S1–S2 level. Dates and sites of disease relapse (local relapse and/or distant relapse) and survival status were also recorded. All patients were fol lowed up routinely every six months after surgery with cross-sectional imaging of the sacrum and alternating a chest x-ray or chest CT scan (for the first four postoperative years). After four years, patients were followed yearly with a chest radiograph. If a patient was not able to return to our institution, the same follow-up recommendations were communicated to the referring physician. In these cases, follow-up data were extracted from the correspondence from the physicians as well as imaging reports.

Radiotherapy has played an increasingly greater role in the treatment of chordoma throughout the last 30 years at our institution and is the biggest change in approach throughout our study period. Advances in technologies (ie, intensity-modulated radiation therapy, passively scattered and, most recently, pencil beam scanning proton therapy) have allowed us to deliver higher doses of radiation with more precision. We found a significantly higher median total dose was delivered after January 2000 than before January 2000 (before 2000: median=50.0 Gy, interquartile range [IQR]=0–65.0; after 2000: median=70.0, IQR=36.2–70.2; p=.013). With the development of navigation in osteotomy around the turn of the century, a two-staged anterior-posterior combined approach resection has become the preferred method for the more extensive sacral tumors at our institution. We therefore used January 2000 as a cut-off value to test the influence of advancements in treatment of oncological outcomes. Typically, a combination of photons and protons are used to conserve resources and to enable the treatment of more patients with protons, especially children who need all proton therapy where most adults can tolerate more.

Data on complications were collected for all patients treated after 2000 (primary tumor, n=47; first time local recurrent tumor, n=20) and included the following: deep infection (culture proven), surgical intervention due to infection, wound dehiscence, partial transabdominal vascularized vertical rectus abdominis myocutaneous (VRAM) flap necrosis, hardware failure, sacral insufficiency fracture, deep venous thrombosis (only for symptomatic patients using ultrasound, no screening was done for deep venous thrombosis (DVT)), pulmonary embolism, and cerebral spinal fluid leak. cerebrospinal fluid leak (CSF) leaks were primarily sown with 6-0 prolene suture, supplemented with fat graft, dural patch, or vascularizes muscle and usually sprayed with fibrin glue.

Statistical analysis

Primary endpoints of the retrospective review were OS, including death from any cause, local relapse-free survival (L-RFS), and distant relapse-free survival (D-RFS). Follow-up time and time to local and distant relapse were measured from the last operation. Patients were stratified by disease status at presentation for comparison of baseline characteristics using Fisher's exact test for categorical variable and the nonparametric Mann-Whitney *U* test (also called Wilcoxon rank-sum test) for continuous variables. The rates of OS, L-FRS, and D-RFS were estimated using Kaplan-Meyer curves. A log-rank was used to test equality of survivor functions. The association between a single variable and OS, L-FRS, and D-RFS was analyzed using bivariate Cox proportional hazards regression analysis for both dichotomous and continuous variables. The relation was estimated using hazard ratios with 95% confidence intervals. Predictors for deep infection were also analyzed using bivariate Cox proportional hazards regression. Variables were considered potential predictors if p value <.10 in the bivariate model. For patients who presented with a primary tumor, all potential confounding predictors were entered into a multivariate Cox proportional hazards regression model to identify factors independently associated with survival, local relapse, or distant relapse. Collinear variables were dropped from the multivariate analysis. No multivariate analysis was performed in the recurrent tumor group due to the small number of patients (N=28). All reported p values were two-tailed and considered statistically significant when p<.05. All statistical analyses were performed using Stata version 13 (Stata Corp., College Station, TX).

Results

Patient and treatment characteristics

The total study population included 101 surgically treated sacral chordoma patients. Of them, 73 (72%)

Table 1
Demographics

	Primary tumors*		First local recurrent tumors†		
	N	%	N	%	p Value
Total	73	-	28	-	-
Sex					
Female	29	40	6	21	.065
Male	44	60	22	79	
Age in years (median, IQR)	61 (50–75)	-	61 (48–73)	-	.630
Treated prior to January 2000					
Yes	29	40	8	29	.210
No	44	60	20	71	
Tumor location‡					
S1	11	15	6	24	.784
S2	21	29	8	32	
S3	17	24	6	24	
S4	10	14	1	4.0	
S5	3	4.2	1	4.0	
Coccyx	10	14	3	12	
Tumor volume in cm^3 (median, [IQR])§,‖	158 (46–634)	-	39 (14–175)	-	**.001**
Tumor histology					
Conventional chordoma	64	88	26	93	.635
Chondroid chordoma	7	10	1	3.6	
Dedifferentiated chordoma	2	2.7	1	3.6	
Pre-op radiation	61	84	17	60	**.016**
Pre-op radiation dose in Gy (median, [IQR])¶	50.0 (20.0–50.4)	-	19.8 (19.8–24.0)	-	**.002**
Surgical management					
Single staged procedure#	59	81	21	75	0.348
Two staged procedure	14	19	7	25	
Level of sacral resection**					
Above S3	46	63	22	79	0.103
Below S3	27	37	6	21	
Intra-op radiation	1	1.4	3	11	0.064
Intra-op radiation dose in Gy (median, [IQR])	3.5 (3.5–3.5)	-	10 (7.5–15)	-	**.029**
Lumbo-pelvic reconstruction performed	10	14	5	18	.403
Ileo- or colostomy placed	17	23	10	36	.156
Surgical margin					
Negative (R0)	58	80	16	57	**.024**
Positive (R1 or R2)	15	21	12	43	
Post-op radiation	42	58	16	57	.573
Post-op radiation dose in Gy (median, [IQR])††	19.8 (19.8–50.4)	-	50.4 (19.9–56.3)	-	.356
Neo- and/or adjuvant chemotherapy	4	6	5	18	.064

* Patients who presented to our institution with a primary tumor and no prior treatment.

† Patients who presented to our institution with a first time recurrent tumor with prior treatment outside of our institution.

‡ The most cephalad sacral vertebrae involved with tumor; data were missing for one (1.4%) primary tumor patient and for one (3.6%) recurrent tumor patient; In two (7.1%) recurrent tumor patients, the tumor was located in the gluteus maxiumus.

§ Volume was calculated using the formula of an ellipsoid mass (volume = $\pi/6 \times$ height $\times$ width $\times$ depth).

‖ Data were missing for 10 (13.7%) primary tumor patients and 2 (7.1%) recurrent tumor patients.

¶ Data were missing for three (4.1%) primary tumor patients.

The patient was either operated on using a single approach (N=47; 68.7%) or the patient was flipped from supine to prone position within the same session (N=20; 29.9%).

** Data were missing for three (4.1%) primary tumor patients and for two (7.1%) recurrent tumor patients.

†† Data were missing for one (1.4%) primary tumor patient.

presented with a primary tumor and no prior treatment. Twenty-eight (28%) of them presented with a first time recurrent tumor after prior treatment elsewhere. Patient and treatment characteristic are outlined in Table 1. Men predominated in both groups (primary: 60%; recurrent: 79%; p=.065) and the median age was the same (primary: 61 years, IQR: 50–75; recurrent: 61 years, IQR: 48–73; p=.630). In both groups, the tumors were mostly conventional chordoma (primary: 64%; recurrent: 93%; p=.635) and located in S2 (primary: 29%; recurrent: 32%; p=.784) but differed in size (primary median size: 158 cm^3, IQR: 46–634; recurrent median size: 39 cm^3, IQR: 14–175; p=.001. Preoperative radiation was more often used in primary tumor patients than in recurrent tumor patients (primary: 84%; recurrent: 60%; p=.016) and with higher dosages (primary median dose:

Table 2
Primary treatment characteristics for recurrent tumors (N=28)

	N	%
Sacral resection*	27	96
Positive surgical margins	22	81
Neo- and/or adjuvant radiation	16	57

* One patient underwent definitive radiotherapy with CyberKnife.

50.0 Gy, IQR: 20.0–50.4; median recurrent dose: 19.8 Gy, IQR: 19.8–24.0). Patients were surgically managed using either a single-stage or a two-staged approach (primary: 81% single stage; recurrent: 75% single stage; p=.348) and most resections were done above the S3 level (primary: 63%; recurrent: 79%; p=.103). Negative surgical margins (R0) were more often achieved in the primary tumor patient (primary: 80%; recurrent: 57%; p=.024). Postoperative radiation was part of treatment in 42 (58%) of the primary tumor patients and 16 (57%; p=.573) of the recurrent tumor patients.

Primary tumors: overall survival

Median follow-up duration after surgery was 69 months (IQR: 44–108). Of the 33 patients who were alive at last moment of follow-up, the median follow-up duration was 64 months (IQR: 48–75). A total of 40 deaths (55%) were observed and the median OS was 86 months. Of them, 24 (60%) died with disease and 7 (18%) died of an unknown cause. Nine patients (23%) died of a known other cause, of whom two died of another cancer. The OS at 5 and 10 years was 79% (95% confidence interval [CI]: 67%–87%; Table 3) and 52% (95% CI: 37%–65%), respectively. On bivariate analysis, tumor size was the only significant predictor for worse OS (hazard ratio [HR]: 1.77; 95% CI: 1.24–2.54; p=.002), and a trend was noted toward worse survival when surgical margins were positive (HR: 1.82; 95% CI: 0.88–1.78; p=.106). There were no significant differences according to patient age, time period of treatment, histology, level of resection, and use of radiation. Multivariate analysis confirmed the results above with tumor size being

Table 3
Outcomes

	OS*		L-RFS†		D-RFS‡	
	5 y % (95% CI)	p Value	5 y % (95% CI)	p Value	5 y % (95% CI)	p Value
Total cohort (N=101)						
Presentation						
Primary (N=73)	79 (67–87)	.341	86 (73–93)	.478	82 (70–89)	.072
Recurrent (N=28)	65 (43–80)		79 (53–92)		64 (42–80)	
Primary tumor patients (N=73)						
Treated prior to January 2000						
Yes (N=29)	76 (55–86)	.334	78 (54–90)	**.044**	92 (72–98)	.199
No (N=44)	81 (66–90)		92 (78–98)		76 (60–86)	
Histology						
Conventional chordoma (N=64)	77 (64–86)	.695	86 (72–93)	.684	82 (69–90)	.288
Other (N=9)	89 (43–98)		86 (33–98)		67 (28–88)	
Level of sacral resection						
Above S3 (N=43)	76 (60–86)	.403	82 (64–92)	.876	80 (64–90)	.878
Below S3 (N=27)	85 (65–94)		96 (76–99)		80 (58–91)	
Surgical margin						
Negative (R0) (N=58)	80 (67–88)	.106	89 (76–96)	.650	78 (64–87)	.554
Positive (R1 or R2) (N=15)	73 (44–89)		73 (37–90)		91 (51–99)	
Neo- and/or adjuvant radiation						
Yes (N=57)	80 (67–89)	.228	88 (74–95)	**.040**	78 (64–87)	.670
No (N=16)	75 (46–90)		76 (72–92)		86 (55–96)	
First local recurrent tumor patients (N=28)§						
Treated prior to January 2000						
Yes (N=8)	73 (28–93)	.686	86 (39–98)	.311	88 (39–98)	.999
No (N=20)	61 (35–80)		76 (43–92)		54 (29–74)	
Surgical margin						
Negative (R0) (N=16)	61 (33–80)	.999	81 (44–95)	.999	71 (40–88)	.931
Positive (R1 or R2) (N=12)	68 (29–88)		76 (30–94)		56 (24–79)	
Neo- and/or adjuvant radiation						
Yes (N=18)	89 (61–97)	.254	76 (48–90)	.062	78 (51–91)	.698
No (N=10)	0		0		0	

* Overall survival.
† Local relapse-free survival.
‡ Distant relapse-free survival.
§ Histology and level or resection were not included due to skewed distributions of patients and few outcomes.

Table 4
Multivariable analysis for primary tumor patients (N=73)

	OS*		L-RFS†		D-RFS‡	
	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
Age	1.0 (0.98–1.1)	.214	0.98 (0.93–1.0)	.593	0.98 (0.94–1.0)	<.427
Size (cm^3)	1.0 (1.0–1.0)	**.004**	0.99 (0.99–1.0)	.413	1.0 (1.0–1.0)	**<.001**
Positive margins	1.1 (0.48–2.4)	.870	2.3 (0.50–10)	.287	0.51 (0.14–1.8)	<.302
Neo- and/or adjuvant radiation	0.68 (0.31–1.5)	.323	0.20 (0.043–0.90)	**.037**	1.9 (0.52–7.0)	<.327

*Overall survival.
†Local relapse-free survival.
‡Distant relapse-free survival.

the only independent predictor for worse OS (HR: 1.68; 95% CI: 1.38–2.42; p=.004; Table 4).

Primary tumor: local recurrence-free survival

A total of 13 (18%) local relapses were observed and the median local recurrence-free survival (L-FRS) was 51 months. The L-FRS at 5 years was 86% (95% CI: 73% –93%; Table 3). On bivariate analysis being treated before January 2000 (HR: 3.93; 95% CI: 1.03–14.9; p=.044) and not receiving radiation were significant predictor for worse L-FRS (HR: 0.27; 95% CI: 0.09–0.80; p=.018; Fig. 1). There were no significant differences according to patient age, tumor size, histology, level of resection, and surgical margins. Multivariate analysis confirmed that not receiving radiation was an independent predictor for worse L-FRS (HR: 0.20; 95% CI: 0.0043–0.90; p=.004; Table 4). Time period of treatment was dropped from the multivariate analysis due to collinearity. There were two cases of lymph node involvement from the beginning and in both cases there were local recurrences.

Primary tumor: distant relapse-free survival

A total of 20 (27%) distant relapses were observed and the median distant relapse-free survival (D-RFS) was 42 months. The D-RFS at 5 years was 82% (95% CI: 70% –89%; Table 3). On bivariate analysis, tumor size was the only significant predictor for worse D-RFS (HR: 2.14; 95% CI: 1.42–3.21; p<.001). There were no significant differences according to patient age, time period of treatment, histology, level of resection, surgical margin, and use of radiation. Multivariate analysis confirmed the results above with tumor size being the only independent predictor for worse D-RFS (HR: 2.25; 95% CI: 1.47–3.44; p<.001; Table 4).

Primary tumor: complications

Of the 47 patients with a primary tumor, 15 (32%) developed a deep infection of whom 13 (87%) were surgically treated. The remaining two patients were treated with antibiotics only and weekly wound care. In bivariate analysis, we found no possible predictors for infection. Five patients

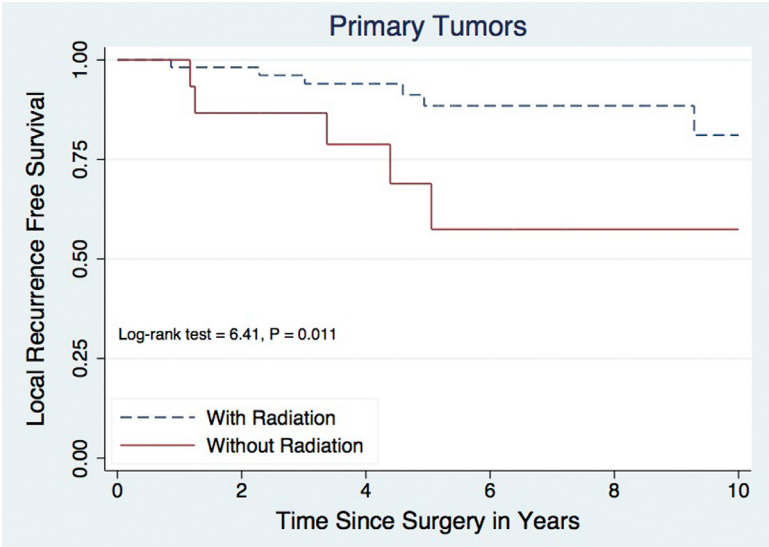

Fig. 1. Kaplan-Meier estimated survivorship curves comparing local recurrence-free survival rates in primary tumor patients who were treated with and without neo- and/or adjuvant radiation. The estimated rates were significantly better for patients treated with radiation (log-rank test=6.41, p=.011).

(16%) had only wound dehiscence and three patients (6%) had a partial VRAM flap necrosis, all needing surgery. Of the 12 patients treated with a lumbo-pelvic reconstruction, two (17%) had hardware failure of whom one (50%) needed surgery. Fourteen patients (30%) had a sacral insufficiency fracture of whom four (29%) needed surgery. Fractures are mostly diagnosed on CT or MRI and are often asymptomatic and therefore not treated. One patient (2%) had a deep venous thrombosis and none a pulmonary embolism. One patient (2%) had cerebral spinal fluid leak also needing surgery.

Patients were admitted for a median of 10 days (range, 1–78 days) during the planned admission. Ten patients (21%) had one unplanned readmission, six patients (13%) had two unplanned admissions, and four patients (9%) had three or more unplanned admissions.

Recurrent tumors: overall survival

Median follow-up duration after surgery was 57 months (IQR: 34–101). Of the 13 patients who were alive at last moment of follow-up, the median follow-up duration was 66 months (IQR: 42–105). A total of 15 deaths (54%) were observed and the median OS was 86 months. Of them 10 (67%) died with disease and 3 (20%) died of an unknown cause. Two patients (13%) died of a known other cause, of who one died of another cancer. The OS at 5 and 10 years was 65% (95% CI: 43%–80%; Table 3) and 40% (95% CI: 19%–61%), respectively. On bivariate analysis, there were no significant differences according to age, tumor size, time period of treatment, surgical margin, and use of radiation.

Recurrent tumor: local relapse-free survival

A total of six (21%) local relapses were observed after initial presentation with locally relapsed disease and the median L-FRS was 44 months. The L-FRS at 5 years was 79% (95% CI: 53%–92%; Table 3). On bivariate analysis, only increased tumor size was a significant predictor for worse L-FRS (LR median: 338 mL; IQR: 218–503 mL; no LR median: 26 mL; IQR: 9–71 mL; p=.001). There were no significant differences according to patient age, time period of treatment, surgical margin, and the use of radiation.

Recurrent tumor: distant relapse-free survival

A total of 13 (43%) distant relapses were observed and the median D-RFS was 30 months. The D-RFS at 5 years was 64% (95% CI: 42%–80%; Table 3). On bivariate analysis, there were no significant differences according to age, tumor size, time period of treatment, surgical margin, and use of radiation.

Recurrent tumor: complications

Of the 20 patients with a first local recurrent tumor, 10 (50%) got a deep infection of whom 9 (90%) needed a surgical intervention as a result. In bivariate analysis, we found the use of neo- and/or adjuvant radiotherapy to be predictive for a higher change on infection (HR 0.06; 95% CI: 0.01–0.33; p value .007). Five patients (36%) had only wound dehiscence and one patient (5%) had a partial VRAM flap necrosis, none needing surgery. Wounds were cleaned weekly in an outpatient setting. Of the four patients treated with a lumbo-pelvic reconstruction, one (25%) had hardware failure of whom one (100%) needed surgery. Six patients (30%) had a sacral insufficiency fracture. One patient (5%) had a deep venous thrombosis and one (5%) a pulmonary embolism during admission and recovered after thrombolysis.

Primary versus recurrent tumor: oncological outcomes

On bivariate analysis, there were no significant differences according to the presentation of the tumor (Figs. 2 and 3). A trend was seen toward better distant relapse survival for tumors presenting as a primary tumor (HR: 0.51; 95% CI: 0.25–1.06; p=.072; Table 3).

Discussion

Sacral chordoma is a rare and difficult to manage tumor. With advancements in surgical techniques, radiotherapy, and chemotherapy, consensus on the optimal treatment remains unclear. We were able to include 101 sacral chordoma patients treated only by orthopedic oncology surgeons at a dedicated chordoma care department of a tertiary referral center. In this series of surgically treated sacral chordomas, the OS at 5 and 10 years was not significantly different for primary tumors versus first local recurrent tumors (79%/59% and 65%/40%, respectively). While primary tumors were significantly larger at presentation than the relapsed local tumors, local relapse-free survival at 5 years was also not different between these groups (86% and 79%). Further, use of radiation therapy reduced risk of local recurrence when treating primary chordoma, regardless of margin or size.

This study has several limitations. First, the current series only presents patients who were surgically treated. Surgical resection has been the standard of treatment and this study will therefore include most sacral chordoma patients treated at our institution. Patients do get treated with definitive high-dose radiation but indications (usually upper sacral tumors with intact bowel and bladder function) are different, which would make for a heterogeneous cohort if grouping all patients together. One of the strengths of the current study is the highly homogenous cohort, including only sacral chordomas treated in a single institution. By analyzing patients presenting with a primary tumor and patients presenting with a first local recurrence separately,

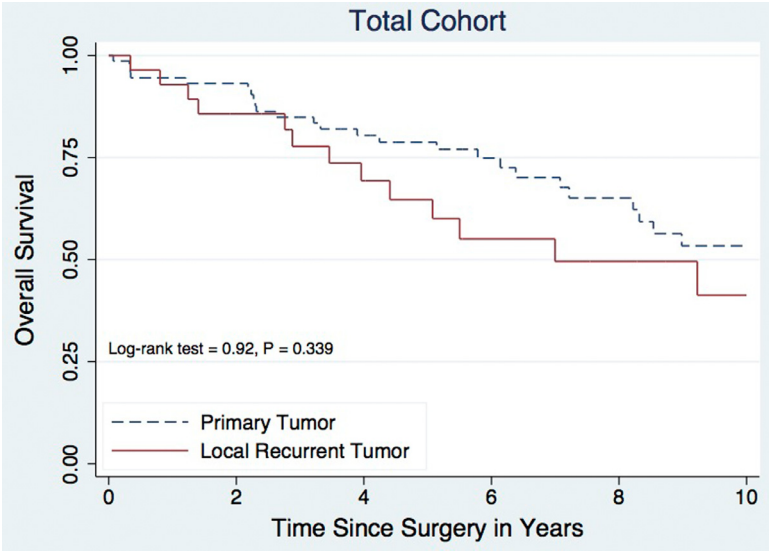

Fig. 2. Kaplan-Meier estimated survivorship curves comparing survival rates between patients who presented with a primary tumor and patient who pretended with a first time local recurrent tumor. The estimated rates were not different (log-rank test=0.92, p=.339).

we further strengthened the homogeneity of the study populations. This is rarely done in sacral chordoma studies due to the rarity of the disease and thus difficulty in obtaining sufficient numbers for analysis. Second, to include as many patients as possible, we included patients who were treated over a 35-year period. During this period, surgical, radiation, and imaging techniques advanced and treatment philosophies changed. This is underscored by the difference in local recurrence-free survival when grouping patients treated before and after January 2000. Yet, this allowed us to compare different treatments given throughout the studies time period. Third, because we were limited to the data available in the orthopedic oncology database and medical records, there were some missing follow-up data. Nevertheless, missing data were within reasonable limits.

To our knowledge, there are no studies comparing presentation and treatments for primary and first local recurrent sacral chordoma tumors within a single institution or through a meta-analysis. For tertiary referral centers, local recurrent tumors referred from an outside institution are a significant proportion (28% in the current study) of the sacral chordoma population [3,4,22,28,31–33,35] and pose a real challenge in terms of treatment. Previous series have analyzed both groups as a whole [2–4,13,14,31–33,35], whereas we analyzed both groups separately. In terms of analysis, when grouping primary and recurrent tumors in one group, one assumes them to be similar at presentation and in terms of treatment. Not surprisingly, we have shown recurrent tumors to be much smaller. Confirmed in the current study, increased tumor size has proved to be a predictor for worse OS, L-RFS, and D-RFS [2,35]. For this reason, we believe it is not appropriate to group primary and recurrent tumors together. Possibly there are other factors (eg, proteomic profiles [6]) that are different in primary and recurrent chordoma patients. Studies have shown previous treatment at an outside hospital to be predictive of worse OS and local recurrence [2,32,33]. One study even excluded previously treated tumors from further analysis due to the severe confounding effect [2]. We also found a lower rate of negative margins when resecting recurrent tumors. An explanation is the increased difficulty to properly expose the tumor due to scar tissue of previous surgeries and radiotherapy, emphasizing the differences in primary and previously treated sacral chordomas. Also, due to the multicentric nature of the tumor, it is difficult to determine the borders.

Our OS rates for primary tumors are comparable with studies reporting specifically on primary sacral chordomas (59%–90% at 5 years and 42%–70% at 10 years [1,5,17,18,20,24,26,27,40,41]). Increased tumor size has not been shown to be an independent predictor for worse OS in patients undergoing surgery, although this has been reported in studies that combined primary and local recurrent chordoma [2,35]. Increased tumor size (>500 cc) has been reported to predict worse survival in unresected mobile spine and sacral chordomas [7]. A series by Hulen et al. [20] showed tumor size to be predictive of local recurrence, where Fuchs et al. [17] did not show this correlation. This was explained by the smaller mean tumor size (9 cm vs. 15.2 cm). Baratti et al. [3] supported this and showed tumor size to also be predictive for increased change of local recurrence. However, these studies did not look at tumor size as a possible predictor for worse OS. Angelini et al. [2] did include tumor size in their analysis on OS and found it to be an independent predictor. The large size at presentation and the complex sacral anatomy decrease the effectiveness of treatment and might account for the high rate of local recurrence and decrease in OS. Negative margins have been shown to influence survival [5,17,32] and showed a trend (p=.106) toward better survival in bivariate analysis.

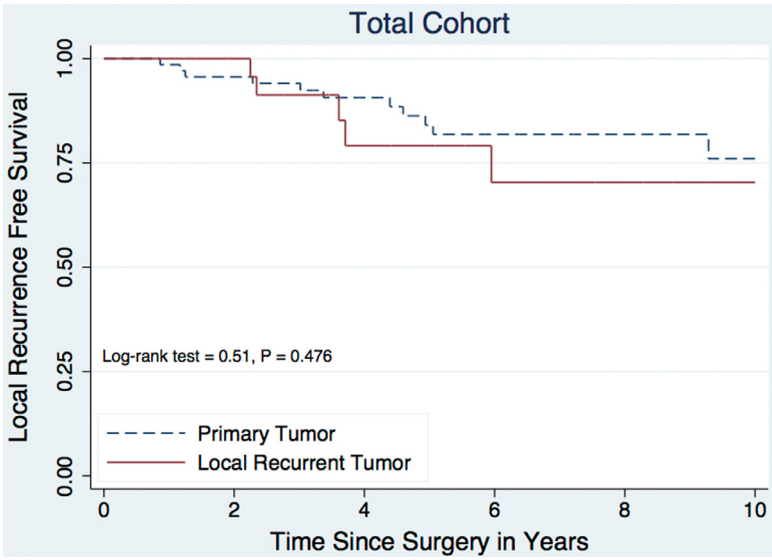

Fig. 3. Kaplan-Meier estimated survivorship curves comparing local recurrence-free survival rates between patients who presented with a primary tumor and patient who pretended with a first time local recurrent tumor. The estimated rates were not different (log-rank test=0.51, p=.476).

Local relapse-free survival for primary sacral chordoma at 5 years ranges from 59% to 100% [17,26,28,31]. In the current study, a L-FRS of 86% at 5 years was achieved. This represents a relatively low number of recurrences possibly owing to the increased use of adjuvant radiotherapy. That adjuvant radiotherapy aids in the local control of primary sacral chordoma was confirmed using multivariate analysis in the current study. This results on local recurrence reported by Ji et al. [22].Their patients, however, were not routinely given radiation; instead, it was reserved mainly for recurrence. The primary tumors that did receive radiation in the Ji et al. study were radiated at an outside institution before being referred for surgical resection. It does not become clear what radiation protocol or dosages were used in any of the radiated patients, making it difficult to reliably interpret these results. The use of adjuvant radiotherapy has been debated over the last decades, but over the last 15 years, it has been fairly consistently used in cases where inadequate margins were achieved [17,19,24,26,27]. With evidence of its effectiveness and safety growing [10–12,29,37], neo- and/or adjuvant radiotherapy in combination with en bloc resection is gaining popularity [13,28,31,35]. A recent study of unresectable sacral chordomas, using only carbon-ion radiotherapy, also showed promising results (5-year local control and OS of 77.2% and 81.1%, respectively) [21]. Patients treated in our series before January 2000 were more likely to recur, probably because the use of high-dose radiation increased after the turn of the century, as we showed by the increase of median dose before and after January 2000 (before 2000: median =50.0 Gy, IQR=0–65.0; after 2000: median=70.0, IQR=36.2–70.2; p=.013). Some chordoma patients treated by a single orthopedic oncology surgeon from 1990 to 2000 (N=10) did not receive radiation but surgery only and all eventually recurred. This suggests that radiation significantly improves the outcome compared to carefully planned surgical procedures done by the same individual. During this period of time, the primary chordoma patients were essentially delegated to the radiation or nonradiation group according to the beliefs of four radiation oncologists of our institution, only three of whom recommended radiation. Even though radiation therapy seems to reduce local recurrence-free survival, it is not without side effects [8,9,25]. These include lymphedema, bone toxicity, and impaired wound healing. Although uncommon, radiation associated sarcoma can also occur [23,30,38]. The current study reports neo- and/or adjuvant radiotherapy to be predictive of deep infection in first time local recurrent tumors. These results must be interpreted with care since they are tested using only bivariate analysis due to the small number of patients.

A total of 27% of the primary tumor patients had a distant relapse, which is comparable with current literature [1,17,20,24,31]. Increased tumor size has been shown to be an independent predictor for distant relapse [35]; this is confirmed in the current study.

Surgical resection of sacral tumors is challenging because of the anatomic complexity of the region. Chordomas can often grow large before becoming symptomatic. After resection, this can leave a big void and have patients be more vulnerable to infection and wound healing problems are common complications. We found readmission to be high in primary tumor patients. These were mostly due to wound problems needing surgical debridement or intravenous antibiotics. To or knowledge, there are no other studies describing readmission rates in this population.

Studies reporting specifically on patients presenting with a local recurrent tumor report OS rates of 50% to 78% at

5 years [28,31,35,40] and 19% to 57% at 10 years [28,32,35,40]. OS rates for patient presenting with first local recurrent tumor were comparable; 65% at 5 years and 40% at 10 years. In terms of local control, we found 79% of the patients to be free of local recurrences at 5 years. This is favorable when compared to current literature that reports local recurrence-free survival of 47% to 57% [28,31,35]. The use of adjuvant radiation might explain the high rate of local recurrence-free survival. The trend toward better local control in patients who received adjuvant radiation supports this. Also, the study with the highest rate of local recurrence-free survival in patients presenting with local recurrence used adjuvant radiation in all their patients [28]. To our knowledge, there is only one study that looked at prognostic factors for second local recurrence, none being identified [35]. We showed that increased tumor size had a negative impact on local control. It is interesting to note that even though tumor size at presentation was smaller than primary tumors, it is still a predictor for local recurrence. Close follow-up and early detection of still relatively small local recurrences could help to increase local relapse-free survival.

When comparing oncological outcomes for primary and recurrent tumor, we did not find any differences. This is in contrast with previous studies [2,22,32], reporting that intralesional resection at an outside institution is associated with an increased risk of local recurrence. It would have been informative if the authors would define the previous intralesional treatment, like Je et al. [22]. Without this definition, previous surgery could range from a recent debulking to a local recurrent tumor after months or years a disease-free period. Even though, in theory, all recurrent tumors left tumor cells behind at the initial surgery even if the initial pathology report stated that negative margins were obtained. For example, in this study, three primary tumors were resected and negative margins were obtained but did eventually recur. This raises a question about the value of negative margins as reported by the pathologist and undermines the idea of using adjuvant radiotherapy only when tumor margins are positive [3,17,19,24,26,27]. Another issue to take into consideration is the potential of lymph node disease. In our series, in a subset of patients treated with surgery and radiation by one surgeon, a total of two patients locally recurred even though negative margins were obtained. Interestingly, both patients were diagnosed with lymph node metastases prior to surgery. Another cause of local recurrence, detected on MRI as seen on in soft tissue sarcomas, is the extent of tumor cells in the edema surrounding the tumor [15].

In conclusion, a combination of surgical resection and adjuvant radiotherapy allowed us to obtain good OS, local relapse-free survival, and distant relapse-free survival in patients presenting with either a primary tumor or a first local recurrence. The use of adjuvant radiotherapy seems to have a positive effect on OS and distant metastases and should be considered as an adjuvant treatment.

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