Chondrosarcomas are among the most frequent primarytumors of bone. They represent a heterogeneous groupof lesions, of which the conventional primary central subtype is the most common (75% to 80%)[1-3]. Conventional chondrosarcomas are histologically classified into grades I to III. Chondrosarcoma is relatively resistant to radiation and chemotherapy, and a surgical procedure therefore remains themainstay of treatment[1-3]. Although curettage with local adju- vants is generally considered a good treatment option for low-grade chondrosarcoma of long bones, most authors recommend resection with clear margins for pelvic chondrosarcoma of any grade[1,4-8].

Traditionally, pelvic bone tumors were treated withhindquarter amputation (also known as external hemipelvec- tomy), a procedure associated with poor functional and cos- metic outcomes[9-12]. Nowadays, most pelvic neoplasms aretreated with a limb-salvaging en bloc resection[13,14]. These in- ternal hemipelvectomies are some of the most challenging procedures in orthopaedic oncology because of the complex pelvic anatomy, the proximity of major neurovascular structures, the fact that pelvic tumors are often large by thetime of diagnosis, and challenges associated with reconstruc- tion[13-17]. As a result, pelvic tumor resections are associated witha substantial risk of contaminated margins[18].

Previous studies on pelvic chondrosarcoma have com- bined different subtypes, although central chondrosarcomas are more often high-grade and appear to have a worse prognosis than secondary peripheral lesions[4,16,19-22]. The aimof this multicenter study was to assess disease-specific and progression-free survival, risk factors for impaired survival, and complications after a surgical procedure in patients treated for a conventional primary central chondrosarcomaof pelvic bone.

Materials and Methods

A total of 170 patients who underwent a surgical procedurefor a conventional primary central chondrosarcoma (grades I to III[1]) of the pelvis from 1985 to 2013 were identifiedthrough our institutional tumor databases. Eight patients (5%)underwent curettage: 4 grade-I intracompartmental tumors(all continuous absence of any evidence of disease duringfollow-up), 1 grade-I tumor with a higher-grade recurrencethat was resected (no evidence of disease at the time of the latestfollow-up), 1 grade-III tumor for which secondary resectionwas performed (no evidence of disease at the time of the latestfollow-up), and 2 grade-I tumors that recurred and eventuallyresulted in disease-related death. To minimize bias, patientswho underwent curettage were excluded from further analysis.This left 162 patients (118 male patients [73%]) with a medianage of 51 years (range, 15 to 78 years) (Table I). All were followed for a minimum of 2 years or until death. The medianfollow-up was 12.6 years (95% confidence interval [CI], 8.4 to 16.9 years). Seventeen (10%) of our patients were included inprevious publications: 9 (6%) in a study by Fiorenza et al.[23] and8 (5%) in a study by Andreou et al.[24]. Institutional review boardapproval was not required for this study.

Tumor grade and size, as well as infiltration of sur- rounding soft tissues and the hip joint, were assessed on pathology reports of the resected specimen. General criteria used to grade the lesions were cellularity, nuclear size, and the presence of abundant hyaline cartilage matrix (indicat- inga low grade) or mucomyxoid matrix and mitoses (higher grade)[1,25]. The tumor was classified as grade I in 30 patients (19%), grade II in 93 patients (57%), and grade III in 39 patients (24%). The median maximal tumor size was 11 cm (range, 2.5 to 25.0 cm) (data were available for 151 patients [93%]). Five patients (3%) had presented with a patholog-ical fracture. Hip (n = 57 [35%]) and sacroiliac joint (n = 14) reconstruction depended on tumor location and surgeon preferences. Primary treatment consisted of internal hemipel- vectomy in 135 patients (83%) and of hindquarter amputationin 27 patients (17%). Hindquarter amputation was only per- formed if it was deemed impossible to obtain clear margins with a limb-salvaging resection, or if 2 or 3 of the following structures had to be resected: hip joint, sciatic nerve, and femoral nerve. The most common types of internal hemipel- vectomy were Type 2-3 (n = 46 [34%]), Type 1 (n = 24 [18%]),Type 3 (n = 17 [13%]), and Type 2 (n = 14 [10%]); 89 (66%) comprised the periacetabulum, 40 (45%) of which were extra-articular resections of the hip[26]. Of 135 hemipelvectomies, 104(77%) were reconstructed, including 60 with metallic implants(58%) (Figs. 1, 2, and 3), 14 with allograft-prosthetic composites (13%), and 10 with allograft reconstructions (10%). The median duration of the surgical procedures was 4.8 hours(range, 1.5 to 10.5 hours) (data were available for 101 patients[62%]).

Surgical margins were classified as wide (resection outsidethe reactive zone) in 83 patients (51%), marginal (resection through the reactive zone, no tumor cells at the margins) in 42patients (26%), and intralesional (tumor cells present at the margins) in 37 patients (23%) (Table II)[27]. Contaminated resec-tions (i.e., those resections in which tumor spill occurred) wereconsidered to be intralesional, regardless of the margins eventuallyachieved. Eight patients (5%) received chemotherapy, and 7 pa-tients (4%) had adjuvant radiation therapy for inadequate mar-gins or local recurrence. The occurrence of local recurrence wasassessed on imaging (usually MRI) and on histopathology in case a further surgical procedure was performed. Kaplan-Meier curves were used to estimate disease- specific survival and progression-free survival. Disease-specific survival was defined as the time from the surgical procedure todisease-related death and was censored at the date of the latestfollow-up or death due to other causes. Progression-free survival was defined as the time from the surgical procedure to local recurrence or metastasis and was censored at the date ofthe latest follow-up or death due to other causes. Prognostic factors were assessed using multivariable Cox proportional hazards models. Categorical variables were compared between groups using chi-square tests; numerical variables were com- pared using Mann-Whitney U tests. Outcomes are expressed inodds ratios (ORs), hazard ratios (HRs), 95% CIs, and p values.Statistical analysis was performed using SPSS version 21 (IBM),with significance set at $p < 0.05$.

Results

*Oncological Outcome and Risk Factors for Impaired Outcome A*t the time of the latest follow-up, 96 patients (59%) were alive: 71 (44%) continuously had no evidence of disease, 19 (12%) had no evidence of disease following treatment of local recurrence or metastasis, and 6 (4%) were alive with disease. Sixty-six patients (41%) died during follow-up: 55 patients (34%) diedfrom disease and 11 patients (7%) died from other causes.

The median disease-specific survival could not be deter-mined because the survival curve did not cross 0.5; the estimatedmean disease-specific survival was 17.6 years (95% CI, 15.5 to 19.6 years) (Fig. 4). The estimated median progression-free survival was 9.3 years (95% CI, 3.3 to 15.3 years). Sixty-two patients (38%) experienced local recurrence: 9 grade-I lesions(30%), 31 grade-II lesions (33%), and 22 grade-III lesions (56%)($p = 0.027$) (Table III). Four recurrent tumors (6% of 62) wereof higher grade than the original tumor.

Recurrent lesions werediagnosed after a median of 1.7 years (95% CI, 0.1 to 27.3 years):36 (58%) within 2 years and 59 (95%) within 5 years.
The risk of disease-related death was 3% (1 of 30) for grade-I tumors, 33% (31 of 93) for grade-II tumors, and 54% (21 of 39) for grade-III tumors. The patient with a grade-I lesion who died of disease had a grade-II recurrence that me- tastasized. Overall, metastases were diagnosed in 48 patients (30%), after a median of 1.9 years (95% CI, 0.1 to 10.6 years).
Of these, 42 (88%) died of disease, 4 (8%) were alive with thedisease at the time of the latest follow-up, and 2 (4%) had no evidence of disease following pulmonary metastasectomy. Therisk of metastasis was 32% (30 of 93) for grade-II tumors and44% (17 of 39) for grade-III tumors with regard to chondrosarcoma grade and recurrence rates[19,23].Ninety-five percent of the recurrences occurred within the first5 years after the surgical procedure. Therefore, we recommendclose follow-up with an annual MRI scan during the first post-operative years (Fig. 6), although the utility and accuracy of MRIscans may be hampered by the presence of metallic implants. Alternatively, a CT scan or fluorine-18 fluorodeoxyglucose pos- itron emission tomography (FDG PET) imaging can be obtained,although less aggressive lesions may not be avid on PET[35].
Although survival rates after marginal and intralesional re-section were nearly identical, wide resection margins were associ-ated with a significant survival advantage. Although wide marginsdo not eliminate the possibility of recurrent disease[19,25,29], marginswere the only treatment-related prognostic factor. After diagnosisof local recurrence, the median survival was 2.4 years for grade-IItumors and 1.3 years for grade-III tumors. These poor survivalrates, combined with the association between margins and the riskof recurrence and disease-related death, underline the importanceof obtaining wide margins during primary resection.
Tumor size was the third most important prognostic factorin our multivariable model; for each centimeter of increase inmaximal tumor size, the risk of disease-related death increased by8%. Others also found an influence of chondrosarcoma size orvolume on oncological outcome, but only performed univariableanalyses[24,36,37]. One study identified a weak influence only on the riskof local recurrence, not survival or metastasis, in multivariableanalyses[23]. The presence of soft-tissue infiltration significantlyinfluenced progression-free survival, but failed to reach significancein our analyses on disease-related death. In contrast to our results,Fiorenza et al. previously reported an influence of soft-tissue in-filtration on survival, but not local recurrence, for chondrosar-comas of the axial and appendicular skeleton[23]. In contrast with anearlier study[24], the prognostic significance of soft-tissue infiltrationand tumor size in our study suggests that both the Enneking system and the American Joint Committee on Cancer (AJCC) classifica-tion appear to be reasonable classification systems for pelvicchondrosarcoma[27,38]. However, neither contain all significant vari-ables that were identified in our study, suggesting a need for a newstaging system, although such a system would need to be validated.
Pelvic resections and reconstructions are notorious for thehigh risk of postoperative complications, of which infection is themost common. Infected pelvic reconstructions may require ag- gressive surgical treatment, including removal of reconstructionmaterials or even, although rarely, hindquarter amputation[39]. Ourinfection rate (19%) is comparable with previously reported rates(18% to 32%)[18,39-43]. The risk of infection was higher for patientsafter endoprosthetic reconstruction, although this increased risk may have been caused by the fact that these surgical pro-cedures were the most extensive and complicated ones.
Our study had a number of limitations. We included pa-tients who were treated in 5 different centers between 1985 and2013. Over the years, available imaging techniques and treatmentmodalities have changed and have likely influenced our results.Moreover, different pathologists have assessed tumor grades andmargins, and these were not reevaluated, although the gradingsystem for chondrosarcoma is inherently subjective and it has

Complications After Surgical Procedures

Ninety-five patients (59%) required further operations. The main indications for reoperations were deep infection (n = 31[19%]), wound problems (n = 20 [12%]), reconstruction-related complications (n = 29 [18%]), and reoperations for localrecurrences (n = 40 [25%]). There was no significant difference(p = 0.532) in infection rates between internal hemipelvectomies(27 [20%] of 135) and hindquarter amputations (4 [15%] of 27). Infection was more common in patients with an endo- prosthetic reconstruction (18 [30%] of 60), compared with patients with other types of reconstruction (8 [18%] of 45) or noreconstruction at all (5 [9%] of 57) (p = 0.014). Thirteen patients (8%) underwent secondary hindquarteramputation: 10 (6%) for locally residual or recurrent tumors, and 3 (2%) for infection. One patient (1%) underwent a type- BII rotationplasty[28] because of infection. Limb salvage was ach-ieved in 121 patients (75%).

Discussion

In this multicenter study, we evaluated oncological outcome,risk factors for impaired survival, and postoperative compli- cations in 162 patients who underwent resection of a pelvicconventional primary central chondrosarcoma. Pelvic chondro-sarcomas are notoriously difficult to treat and are more often ofhigh grade, and treatment has been associated with worse out-comes than those of extremity chondrosarcoma[16,24,29]. Thirty-fourpercent of our patients died of disease. Other series on pelvic chondrosarcoma have shown that 20% to 36% of patients diedfrom disease[4,16,20,21], but these included different subtypes and primary central lesions appear to have a worse prognosis thansecondary peripheral tumors[4,19,21,22].
In concordance with previous studies, tumor grade was themost important prognostic factor for patient survival[4,16,19,21,22,30] (Table V). Of the patients with a grade-I lesion on the resectionspecimen, only 1 (3%) died of disease. Limited surgery may seemattractive for these low-grade pelvic chondrosarcomas, given theexcellent survival rates and the favorable clinical outcome reportedfor curettage of low-grade extremity chondrosarcoma[7]. However,several problems remain to be solved. First, recurrent tumors canbe of higher grade than the initial lesion, and recurrence may beregarded as a declaration of a more aggressive subtype[4,5,31,32]. In thecurrent series, 4 recurrences (6% of 62) were of higher grade thanthe initial tumor. Second, part of a lesion that appears to be grade Ion the basis of a biopsy specimen may actually be of higher gradeon the resected specimen[33,34]. Third, curettage has been associatedwith unacceptably high recurrence rates in previous series on pelvic chondrosarcoma[5,32]. Many authors therefore have recom- mended resection with clear margins for pelvic chondrosarcomaof any grade[1,4-6]. As long as it is not possible to reliably distinguishbetween grade-I lesions and higher-grade lesions preoperatively, we concur with previous authors stating that en bloc resection is the preferable treatment option for pelvic chondrosarcoma[5,32].
Tumor grade was also found to be associated with the riskof tumor recurrence. Previous studies showed conflicting results been shown

that the interobserver reliability of this classification is poor[33,34]. However, we only included patients from referral centers with specialized pathologists, and, because of the rarity of this disease, multicenter cooperation is necessary to gain sufficient power. Further research is needed to develop techniques to reliably determine tumor grade and clinical behavior preoperatively, potentially using molecular markers[1]. Also, further study should be directed at the role of limited surgical procedures for low-grade chondrosarcoma of the pelvis. Moreover, the exact margin needed to adequately treat pelvic chondrosarcoma, especially grade-I lesions, will have to be determined in a prospective study.

Patients with a local recurrence had a higher risk of metastases (32 [52%] of 62 compared with 18 [18%] of 100; OR, 4.3 [95% CI, 2.1 to 8.7]; $p < 0.001$) and disease-related death (39 [63%] of 62 compared with 16 [16%] of 100; OR, 8.9[95% CI, 4.2 to 18.7]; $p < 0.001$). Measured from the diagnosisof the local recurrence, the median disease-specific survival was 2.4 years (95% CI, 1.4 to 3.4 years) for patients with a grade-IItumor and 1.3 years (95% CI, 0.9 to 1.7 years) for patients witha grade-III lesion (Fig. 5). Of 62 patients with local recurrence,30 (48%) developed metastases, compared with 18 (18%) of 100 patients without local recurrence (OR, 4.27 [95% CI, 2.09to 8.71]; $p < 0.001$).

In our multivariable Cox proportional hazards model, wefound that higher tumor grade, poorer resection margins, and larger tumor size significantly impaired ($p < 0.05$) disease- specific and progression-free survival. In addition, soft-tissue infiltration significantly impaired progression-free survival ($p = 0.024$) (Table IV). Patient sex did not significantly influence survival. The risk of intralesional margins was lower for patientswith a maximal tumor diameter of <10 cm (6 [10%] of 58) thanfor those with a maximal tumor diameter of ‡10 cm (28 [30%]of 93) ($p = 0.005$). Although the risk of contaminated marginswas higher after internal hemipelvectomy (35 [26%] of 135)
than after hindquarter amputation (2 [7%] of 27), hemipel-vectomy type did not significantly influence outcome ($p > 0.05$).

In conclusion, this study offers a standard for survival ratesfor conventional primary central chondrosarcoma of the pelvis.Survival is excellent for patients with a grade-I tumor and a limitedsurgical procedure may therefore seem attractive, although wecannot draw conclusions in that regard. However, higher-gradetumors have a substantial risk of disease-related death. We dem-onstrated that wide resection margins offer a significant survivaladvantage over marginal and intralesional resection for grade-IIand grade-III tumors. Because of the inability to reliably distin-guish low-grade and high-grade tumors preoperatively, we con-clude that any central pelvic chondrosarcoma should be treatedwith aggressive primary resection with the aim of obtaining wideresection margins, understanding that there may be aggressivebiologic features in some tumors for which a surgical procedurealone may not be adequate to improve outcomes.

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