Chondrosarcomas are among the most frequent primary tumors of bone. They represent a heterogeneous group of lesions, of which the conventional primary central subtype is the most common (75% to 80%). Conventional chondrosarcomas are histologically classified into grades I to III. Chondrosarcoma is relatively resistant to radiation and chemotherapy, and a surgical procedure therefore remains the mainstay of treatment. Although curettage with local adjuvant therapy 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.

Traditionally, pelvic bone tumors were treated with hindquarter amputation (also known as external hemipelvectomies), a procedure associated with poor functional and cosmetic outcomes. Nowadays, most pelvic neoplasms are treated with a limb-salvaging en bloc resection. These internal 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 the time of diagnosis, and challenges associated with reconstruction. As a result, pelvic tumor resections are associated with a substantial risk of contaminated margins.

Previous studies on pelvic chondrosarcoma have combined different subtypes, although central chondrosarcomas are more often high-grade and appear to have a worse prognosis than primary peripheral lesions. The aim of 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 chondrosarcoma of pelvic bone.

Materials and Methods

A total of 170 patients who underwent a surgical procedure for a conventional primary central chondrosarcoma (grades I to III) of the pelvis from 1985 to 2013 were identified through our institutional tumor databases. Eight patients (5%) underwent curettage; 4 grade-I intracompartmental tumors (all continuous absence of any evidence of disease during follow-up), 1 grade-I tumor with a higher-grade recurrence that was resected (no evidence of disease at the time of the latest follow-up), 1 grade-III tumor for which secondary resection was performed (no evidence of disease at the time of the latest follow-up), and 2 grade-I tumors that recurred and eventually resulted in disease-related death. To minimize bias, patients who underwent curettage were excluded from further analysis. This left 162 patients (118 male patients [73%]) with a median age of 51 years (range, 15 to 78 years) (Table I). All were followed for a minimum of 2 years or until death. The median follow-up was 12.6 years (95% confidence interval [CI], 8.4 to 16.9 years). Seventeen (10%) of our patients were included in previous publications: 9 (6%) in a study by Fiorenza et al., and 5 (5%) in a study by Andreou et al. Institutional review board approval was not required for this study.

Tumor grade and size, as well as infiltration of surrounding 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 (indicative of low grade) or mucoid round matrix and mitoses (higher grade). 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) for 151 patients (93%). Five patients (3%) had presented with pathologic fractures. Hip (n = 57 [35%]) and sacroiliac joint (n = 14) reconstruction depended on tumor location and surgeon preferences. Primary treatment consisted of internal hemipelvectomies in 135 patients (83%) and of hindquarter amputation in 27 patients (17%). Hindquarter amputation was performed only 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 hemipelvectomies 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. Of 135 hemipelvectomies, 104 (77%) were reconstructed, including 60 with metallic implants (58%) (Figs. 1, 2, and 3), 14 with allograft-osteoprosthesis 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 outside the reactive zone) in 83 patients (51%), marginal (resection through the reactive zone, no tumor cells at the margins) in 42 patients (26%), and intrasosseous (tumor cells present at the margins) in 37 patients (23%) (Table II). Contaminated resections (i.e., those in which tumor spill occurred) were considered to be intralesional, regardless of the margins eventually achieved. Eight patients (5%) received chemotherapy, and 7 patients (4%) had adjuvant radiation therapy for inadequate margins or local recurrence. The occurrence of local recurrence was assessed 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 to disease-related death and was censored at the date of the latest follow-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 of the 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 compared using Mann-Whitney U tests. Outcomes are expressed in odds 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 At 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%) died from 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 estimated mean 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). Fifty-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) were of higher grade than the original tumor.
Recurrent lesions were diagnosed 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 metastasized. 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 the disease at the time of the latest follow-up, and 2 (4%) had no evidence of disease following pulmonary metastasectomy. Thirsk of metastasis was 32% (30 of 93) for grade-II tumors and 44% (17 of 39) for grade-III tumors with regard to chondrosarcoma grade and recurrence rates. Ninety-five percent of the recurrences occurred within the first 5 years of the surgical procedure. Therefore, we recommend close follow-up with an annual MRI scan during the first post-operative years (Fig. 6), although the utility and accuracy of MRIs may be hampered by the presence of metallic implants. Alternatively, a CT scan or 18-fluorine-18 fluoro-deoxylucose post-CT emission tomography (FDG PET) imaging can be obtained, although less aggressive lesions may not be evident on PET.

Although survival rates after marginal and intralvesional resection were nearly identical, wide resection margins were associated with a significant survival advantage. Although wide margins do not eliminate the possibility of recurrent disease, margins were the only treatment-related prognostic factor. After diagnosis, the median survival was 2.4 years for grade-II tumors and 1.3 years for grade-III tumors. These poor survival rates, combined with the association between margins and the risk of recurrence and disease-related death, underline the importance of obtaining wide margins during primary resection. Tumor size was the third most important prognostic factor in our multivariable model: for each centimeter of increase in maximal tumor size, the risk of disease-related death increased by 8%. Others also found an influence of chondrosarcoma size on ultrasound outcome, but only performed univariable analyses. One study identified a weak influence only on the risk of local recurrence, not survival or metastasis, in multivariable analyses. The presence of soft-tissue infiltration significantly influenced progression-free survival, but failed to reach significance in our analyses on disease-related death. In contrast to our results, Fiorenza et al. previously reported an influence of soft-tissue infiltration on survival, but not local recurrence, for chondrosarcomas of the axial and appendicular skeleton. In contrast with an earlier study, the prognostic significance of soft-tissue infiltration and tumor size in our study suggests that both the Enneking system and the American Joint Committee on Cancer (AJCC) classification appear to be reasonable classification systems for pelvic chondrosarcoma. However, neither contain all significant variables that were identified in our study, suggesting a need for a new staging system, although such a system would need to be validated.

Pelvic resections and reconstructions are notorious for the high risk of postoperative complications, of which infection is the most common. Infected pelvic reconstructions may require aggressive surgical treatment, including removal of reconstruction materials or even, although rarely, hindquarter amputation. Our infection rate (19%) is comparable with previously reported rates (18% to 32%) 1-4. The risk of infection was higher for patients after endoprosthetic reconstruction, although this increased risk may have been caused by the fact that these surgical procedures were the most extensive and complicated ones.

Our study had a number of limitations. We included patients who were treated in 5 different centers between 1985 and 2013. Over the years, available imaging techniques and treatment modalities have changed and have likely influenced our results. Moreover, different pathologists have assessed tumor grades and margins, and these were not reevaluated, although the grading system 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 local recurrence (n = 40 [25%]). There was no significant difference 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 endoprosthesis 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 hindquarter amputation: 10 (6%) for locally residual or recurrent tumors, and 3 (2%) for infection. One patient (1%) underwent a type-BII rotationplasty because of infection. Limb salvage was achieved in 121 patients (75%).

Discussion

In this multicenter study, we evaluated oncological outcome, risk factors for impaired survival, and postoperative complications in 162 patients who underwent resection of a pelvic conventional primary central chondrosarcoma. Pelvic chondrosarcomas are notoriously difficult to treat and are often of high grade, and treatment has been associated with worse outcomes than those of extremity chondrosarcoma. Thirty-four percent of our patients died of disease. Other series on pelvic chondrosarcoma have shown that 20% to 36% of patients died of disease, but these included different subtypes and primary central lesions appear to have a worse prognosis than secondary primary tumors. In concordance with previous studies, tumor grade was the most important prognostic factor for patient survival (16,19,21,22,30) (Table V). Of the patients with a grade-I lesion on the resection specimen, only 1 (3%) died of disease. Limited surgery may seem attractive for these low-grade pelvic chondrosarcomas, given the excellent survival rates and the favorable clinical outcome reported for resection of low-grade extremity chondrosarcoma. However, several problems remain to be solved. First, recurrent tumors can be of higher grade than the initial lesion, and recurrence may be regarded as a declaration of a more aggressive subtype. In the current series, 4 recurrences (6% of 62) were of higher grade than the initial tumor. Second, part of a lesion that appears to be grade I on the basis of a biopsy specimen may actually be of higher grade on the resected specimen. Third, curtailment has been associated with unacceptable high recurrence rates in previous series on pelvic chondrosarcoma. Many authors therefore have recommended resection with clear margins for pelvic chondrosarcomas of any grade. As long as it is not possible to reliably distinguish between 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.

Tumor grade was also found to be associated with the risk of tumor recurrence. Previous studies showed conflicting results been shown
that the interobserver reliability of this classification is poor\textsuperscript{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\textsuperscript{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 diagnosis of the local recurrence, the median disease-free survival was 2.4 years (95% CI, 1.4 to 3.4 years) for patients with a grade-I tumor and 1.3 years (95% CI, 0.9 to 1.7 years) for patients with a 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, 2.09 to 8.71]; p < 0.001).

In our multivariable Cox proportional hazards model, we found 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 patients with a maximal tumor diameter of >10 cm (610% of 58) than for those with a maximal tumor diameter of ≥10 cm (28 [30%] of 93) (p = 0.005). Although the risk of contaminated margins was higher after internal hemipelvectomy (35 [26%] of 135) than after hindquarter amputation (2 [7%] of 27), hemipelvectomy type did not significantly influence outcome (p > 0.05). In conclusion, this study offers a standard for survival rates for conventional primary central chondrosarcoma of the pelvis. Survival is excellent for patients with a grade-I tumor and a limited surgical procedure may therefore seem attractive, although we cannot draw conclusions in that regard. However, higher-grade tumors have a substantial risk of disease-related death. We dem-onstrated that wide resection margins offer a significant survival advantage over marginal and intralesional resection for grade-II and grade-III tumors. Because of the inability to reliably distinguish low-grade and high-grade tumors preoperatively, we con-clude that any central pelvic chondrosarcoma should be treated with an aggressive primary resection with the aim of obtaining wide resection margins, understanding that there may be aggressive biologic features in some tumors for which a surgical procedure alone may not be adequate to improve outcomes.

Reference
