Chondrosarcoma of the Phalanx: A Locally Aggressive Lesion with Minimal Metastatic Potential

A Report of 35 Cases and a Review of the Literature

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BACKGROUND. Enchondroma is the most common primary benign bone tumor of the hand, especially the phalanges, whereas chondrosarcoma is uncommon at this site. Although phalangeal chondrosarcoma may have ominous histologic features, its biologic behavior is relatively indolent.

METHODS. Thirty-five cases of phalangeal lesions previously diagnosed as chondrosarcoma were studied. Histologic and tumor-biologic parameters (Ki-67 and p53 immunohistochemistry) were investigated and correlated with clinical behavior.

RESULTS. All cases were characterized by unequivocal malignant histologic features (Grade 2 or higher) or Grade 1 malignant histologic features combined with the presence of cortical destruction and soft tissue extension. The median age of the patients at the time of diagnosis was 67 years (range 21–87 years), with a slight female predominance. Occurrence in the hand was more common than in the foot, with the proximal phalanx affected most often. Treatment varied from local therapy (curettage or local excision) in 16 patients to amputation or exarticulation in 19 cases. Follow-up ranged from 8–432 months for 28 patients. Ten of 15 tumors treated by local therapy recurred whereas none of 13 tumors treated by radical surgery recurred. The median survival was 20.8 years; none of 28 patients developed metastases nor died of disease. Both the type of treatment and localization in the proximal phalanx were associated independently with local recurrence.

CONCLUSIONS. Phalangeal chondrosarcoma behaves as a locally aggressive lesion and, in contrast to chondrosarcomas located elsewhere, rarely metastasizes. Treatment is indicated only because of its locally destructive growth. The authors believe that given the excellent survival data, curettage with adequate follow-up should be considered as the treatment of choice if technically feasible, especially in those cases in which amputation would lead to a significant loss of hand function.


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KEYWORDS: phalangeal chondrosarcoma, bones, hands and feet, phalanx, chondrosarcoma, cartilaginous lesions.

Enchondroma is the most common primary benign skeletal neoplasm of the hand, located predominantly in the phalanges. In contrast, its malignant counterpart is uncommon at this site. Approximately 10% of all chondrosarcomas are located in the bones of the hands and feet, approximately 50% of which are reported to be located in the phalanges.1 Fifty-four percent of all bone tumors of the hand are cartilaginous,2 < 2% of which appear to be malignant.2,3

In general, chondrosarcomas are slowly growing tumors characterized by a late onset of metastases. Little is known regarding the
biologic behavior of chondrosarcomas with a phalan-geal localization, although a relatively favorable prog-nosis has been suggested. To our knowledge only small numbers of cases with limited follow-up, or phalangeal chondrosarcoma forming part of a larger cohort concerning chondrosarcoma of small bones, have been described to date.4,5

The distinction between a benign and malignant cartilaginous tumor of the phalanx at the microscopic level is difficult. It is known that enchondromas of the hands and feet display greater cellularity and nuclear atypia than is sustained elsewhere. Because of the contrast between the frequent ominous histologic appearance of these tumors and their favorable biologic discrepancy behavior, we studied 35 phalangeal cartilaginous lesions that previously were diagnosed as malignant. All were characterized by unequivocal malignant histologic features (Grade 2 or higher according to the system of Evans et al.6) or Grade 1 malignant histologic features combined with the presence of cortical destruction and soft tissue extension. Histologic and biologic parameters were investigated to better define chondrosarcoma of the phalanges and clinical and follow-up data were collected.

MATERIALS AND METHODS

Patient Data
Thirty-eight cases of phalangeal cartilaginous tumors previously diagnosed as chondrosarcoma from 30 different contributing institutions were collected for a retrospective study. Cases were retrieved from the files of the Netherlands Committee on Bone Tumors, which contains > 11,500 bone tumors collected over the past 45 years. Radiographs were reviewed. Dedifferentiated, mesenchymal, juxtacortical, clear cell, and soft tissue chondrosarcomas were not included because of their generally recognized specific clinicopathologic features. Detailed clinical data were collected for each case. Follow-up data were updated by contacting the treating physicians. If no recent follow-up data could be retrieved, survival data were gathered using local government death records.

Histology
Histologic slides were available for all cases and were reviewed by two specialist bone tumor pathologists (P.C.W.H. and R.O.H.) to confirm each diagnosis. Cases were graded according to the system of Evans et al.,6 an established grading system for chondrosarcomas, to compare phalangeal chondrosarcoma with chondrosarcomas located elsewhere in the skeleton. Histologic parameters scored included binucleated cells (<1/1-5/ >5 per high-power fields), nuclear pleomorphism (low/moderate/high), cellular distribution (regular/irregular), cellularity (moderate/focal high/diffuse high), bone formation (absent/focal/diffuse), calcification (absent/focal/diffuse), encasement (defined as new shells of reactive bone at the periphery of cartilage nodules7) (absent/focal/diffuse), entrapment (defined as the permeation of preexisting host bone by tumor7) (absent/focal/diffuse), differentiation (percentage chondroid, mucoid, and myxoid differentiation), and cortical destruction (absent/present/unobservable). For three cases specimens arising from local recurrence were used. For comparison, hematoxylin and eosin stained slides of 16 central Grade 2 chondrosarcomas located elsewhere in the skeleton (femur [n = 7], sternum, metacarpal bone, acetabulum, skull, acromion, costae, tibia, scapula, and pelvis [n = 1 each]) and 8 enchondromas located in the phalangeal bones were scored similarly. For one of the only two cases in the literature in which metastases developed4,8 (described by Cruickshank in 1945,9), paraffin blocks were kindly provided by Professor Walker of Aberdeen University for review and immunohistochemistry.

Immunohistochemistry
Formalin fixed, paraffin embedded tissue was available for 22 specimens from 21 patients. For comparison, formalin fixed, paraffin embedded tissue from 8 enchondromas of the phalanx and 17 chondrosarcomas located elsewhere in the skeleton (Grade 1 [n = 3], Grade 2 [n = 8], and Grade 3 [n = 6]) were stained. Monoclonal antibodies against Ki-67, clone MIB-1 (Immunotech SA, Marseilles, France), and p53, clone DO-7 (Dakopatts, Glostrup, Denmark) were used. Immunohistochemical reactions were performed according to standard laboratory methods.9 Ki-67 positive nuclei were counted per 200 tumor cells in areas containing the largest number of positive cells. Hematopoietic cells in bone marrow or skin served as an internal control. For p53 staining, both staining intensity (1 = weak, 2 = moderate, and 3 = strong intensity) and the percentage of positive cells (1 = 0–25%, 2 = 25–50%, 3 = 50–75%, and 4 = 75–100% positive tumor cells) were evaluated and a sum ≥ 4 was regarded as positive.

Meta-Analyses Literature
Sixty-seven cases reported in the literature dating back to 19348,10–33 were analyzed for comparison with the current series. Dedifferentiated, mesenchymal, juxtacortical, clear cell, and soft tissue chondrosarcomas were excluded. The majority of the data reported in two recent articles4,5 describing larger series including 9 and 28 cases of phalangeal chondrosarcoma, respectively, could not be included in the analysis due to the
fact that only an incidental distinction between metacarpal or metatarsal and phalangeal localization was made.

Statistical Analysis
Histologic parameters were analyzed using the Fisher exact test or the chi-square test for trend and the Mann–Whitney U test. Association between parameters and recurrence was studied for 28 patients using Kaplan–Meier survival curves and the log rank test. Cox survival analysis was used to study the effect of several parameters simultaneously on disease free survival. The median survival and disease free survival times were obtained from Kaplan–Meier survival curves.

RESULTS
Patient Data
Diagnosis
Of 38 cases, 35 were characterized by unequivocal malignant histologic features: Grade 2 (according to the system of Evans et al.6) (n = 27) or Grade 1 malignant histologic features combined with the presence of unequivocal cortical destruction (complete cortical breakthrough) and soft tissue extension as defined on X-rays or documented in the histologic slides (n = 8) (Fig. 1). These 35 cases thus were regarded as malignant and were included in the analysis. Two other patients were excluded from the series of 38 because on review the tumors were diagnosed as dedifferentiated chondrosarcoma, in which a highly anaplastic sarcoma was observed next to a low grade malignant cartilaginous tumor, and chondroblastic osteosarcoma, in which the formation of tumor bone was evident next to pure cartilage-forming areas. In addition, one patient was excluded because of a metacarpal localization.

Radiologic characteristics
Of the remaining 35 cases, phalangeal localization was confirmed. Radiographically, phalangeal chondrosarcoma presented most often as an osteolytic, lobulated tumor with intrasional calcifications and ill-defined margins with cortical destruction and soft-tissue extension (Fig. 2).

Patient characteristics
Clinical data are depicted in Table 1. The median age at diagnosis was 67 years (range 21–87 years) (Fig. 3). Gender distribution showed a slight predilection for females (21 vs. 14). Presenting symptoms included pain and enlargement of a preexisting lesion. The median duration of symptoms before diagnosis was 18 months (range 1–480 months). Four patients presented with multiple enchondromas. The median greatest dimension of the tumors was 3.0 cm (range 1–8 cm). Five cases were documented to be secondary to a preexisting enchondroma, one of which was found in a patient with multiple enchondromas. Treatment varied from marginal therapy for 16 patients (curettage [n = 10] or local resection [resection through affected bone] [n = 6]) to radical excartilation or amputation (resection through the joint) at different levels for 19 patients.

Localization
The tumors occurred far more frequently in the hand compared with the foot and exhibited an equal distri-
Histology

Retrospective grading of the 35 cases was performed strictly according to the criteria of Evans et al. (8 cases were Grade 1, 26 cases were Grade 2, and 1 case was Grade 3), which revealed a difference of nearly 1 grade compared with grading at the time of the original diagnosis. This appears to indicate that pathologists grading phalangeal chondrosarcoma in the first instance took the relatively favorable prognosis into account. Review of the case demonstrating metastasis by Cruickshank confirmed the diagnosis of a Grade 2 chondrosarcoma, both in the primary tumor as well as in the metastatic lesion.

Comparison of histologic parameters scored in both enchondroma and chondrosarcoma with phalangeal localization revealed a clear histologic difference. Parameters that were indicative of malignancy were a high number of binucleated cells (P = 0.007), nuclear pleomorphism (P = 0.001), irregular distribution (P = 0.000), high cellularity (P = 0.002), absence of encasement (P = 0.000), presence of entrapment (P = 0.001), cortical destruction (P = 0.002), and mucoid and myxoid changes (P = 0.003 and P = 0.000, respectively) partly replacing a chondroid differentiation pattern (P = 0.000) (Fig. 5).

Comparison of Grade 2 phalangeal chondrosarcoma with Grade 2 chondrosarcoma located else-

where demonstrated similar histologic features except for reactive bone formation ($P = 0.019$) and matrix calcification ($P = 0.004$), which were more intense in phalangeal chondrosarcomas. Mucoid changes ($P = 0.049$) and entrapment ($P = 0.004$) were less intense in phalangeal chondrosarcomas.

**Immunohistochemistry**

**Ki-67 immunohistochemistry**

Of 22 tumors studied, 2 cases could not be evaluated due to repeated loss of tissue attachment during microwaving procedures. Three tumors had a negative internal control and were excluded; prolonged decalcification most likely was responsible for the antigen destruction in these cases. Seventeen cases remained for analysis, showing a mean Ki-67 index of 6%. Results are depicted in Table 2. The mean Ki-67 index in Grade 2 phalangeal chondrosarcomas appeared lower than in Grade 2 chondrosarcomas located elsewhere ($P = 0.05$). Grade 1 tumors showed a similar trend, but the numbers of cases were too small for meaningful statistical analyses.

**p53 immunohistochemistry**

Of 22 tumors, 3 could not be evaluated due to the technical problems mentioned earlier. Six tumors were positive for p53 staining. The results are summarized in Table 3. The Grade 2 chondrosarcoma that was metastatic showed p53 immunoreactivity. Although not statistically significant, the percentage of p53 positive phalangeal chondrosarcomas appeared slightly lower than in chondrosarcomas of similar grades located elsewhere ($P = 0.39$).

**Follow-up Data**

Follow-up data were available for 28 patients (Table 4). For seven patients, no follow-up data were available. The median follow-up, as counted from the date of first treatment, was 6.6 years (range 8–324 months) for 28 patients and the median survival period was

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**TABLE 2**

Results of Ki-67 Immunohistochemistry

<table>
<thead>
<tr>
<th>Enchondroma</th>
<th>Chondrosarcoma in the phalanx</th>
<th>Chondrosarcoma elsewhere</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>Index</td>
<td>Grade</td>
</tr>
<tr>
<td>7</td>
<td>3.36</td>
<td>Total</td>
</tr>
<tr>
<td>3</td>
<td>2.33</td>
<td>Grade 1</td>
</tr>
<tr>
<td>13</td>
<td>8.5</td>
<td>Grade 2</td>
</tr>
<tr>
<td>1</td>
<td>10.5</td>
<td>Metast</td>
</tr>
</tbody>
</table>

*metast: metastatic.*

“No.” indicates the number of cases that could be evaluated. “Index” is the mean Ki-67 index (percentage of Ki-67 positive tumor cells). The Ki-67 index in both control groups corresponded to similar studies described in the literature.39
20.8 years after first treatment (obtained from the Kaplan–Meier survival curve). The median disease free interval was 12 years (obtained from the Kaplan–Meier survival curve). For 9 patients the follow-up period was 10 years. Four patients required additional surgery for residual tumor tissue. Ten of 15 tumors treated by marginal therapy recurred with a mean interval of 39.3 months (median 24 months). Four patients also experienced a second recurrence. The only patient who did not undergo extensive surgery for a second recurrence developed two additional recurrences. In contrast, none of the patients treated by extended therapy developed a local recurrence. A highly significant association between local treatment and recurrence during follow-up was found (P = 0.0013) (Fig. 6A). This correlation was reinforced when cases from the literature were added (P = 0.0000) (Fig. 6B). Localization to the proximal phalanx also was associated with local recurrence (P = 0.01, adding cases from the literature: P = 0.0061) (Fig. 6C). Cox survival analysis for all cases, including those from the literature, showed that both parameters had an independent effect on disease free survival (treatment: P = 0.0000 and localization: P = 0.0397) (Fig. 6D). Localization in the first ray was not associated with local recurrence. Histologic features, immunohistochemical parameters, and histologic grading were not found to be associated with local recurrence.

**DISCUSSION**

Little is known regarding the biologic behavior of chondrosarcomas located in the phalangeal bones. Ogose et al. reviewed 163 chondrosarcomas located in the phalangeal, (meta-) carpal, and (meta-) tarsal bones of the hands (n = 88) and feet (n = 75) and demonstrated that these tumors as a group have the potential to be fatal. Chondrosarcomas of the calcaneus and the talus were more likely to metastasize. In the current study we presented clinical, histologic, and immunohistochemical data from 35 cases of strictly phalangeal chondrosarcoma.

Establishing a diagnosis of malignancy at a phalangeal location remains extremely difficult. For chondrosarcomas elsewhere, it has been shown that radiographic features displayed on conventional X-rays do not improve the ability to differentiate between enchondroma and Grade 1 chondrosarcoma. In our series, all 35 tumors that previously were diagnosed as malignant were characterized by unequivocal malignant histologic features (Grade 2 or higher according to the criteria of Evans et al.). Grade 1 malignant histologic features combined with the presence of cortical destruction and soft tissue extension. In addition the current study shows that grading according to the system of Evans et al. for prognostic purposes is not useful in phalangeal chondrosarcoma because the metastatic rate is extremely low; no correlation with disease free survival was found. However, a correlation with the metastatic potential for chondrosarcomas elsewhere is well established.
Originally, 38 cases of phalangeal chondrosarcoma were collected. On histologic revision, two cases were diagnosed as dedifferentiated chondrosarcoma and chondroblastic osteosarcoma, respectively. Both patients developed metastases and died shortly after diagnosis. Similarly, mesenchymal chondrosarcoma of the proximal phalanx of the foot was reported to metastasize.35 Although extremely rare at this site, these tumors should be excluded by a thorough histologic examination because they have a clear potential to be fatal.

In our series of 35 cases as well as in the literature, phalangeal chondrosarcoma appears to have a slight preference for females. This is in contrast with chondrosarcomas located elsewhere in the skeleton, in which > 50% of the patients are male.1,6 Furthermore, the median age (67 years) was higher than for chondrosarcomas in general (Grade 1: 44 years and Grade 2: 55 years).1 The age incidence rate in our study showed a fairly even distribution, which is in contrast to data from the literature regarding phalangeal chondrosarcoma and chondrosarcoma in general. This may be due to our series originating from a national bone tumor registry and not from a single referral center.

None of our patients developed metastases or died of tumor-related disease. Combining our data with those from the literature, of a total number of 112 phalangeal chondrosarcoma patients, only 2 (1.8%) developed metastases (median follow-up of 4.5 years), of which the diagnosis could be confirmed in 1 patient. However, it cannot be ruled out completely that these two cases represent chondroblastic osteosarcoma or dedifferentiated chondrosarcoma, which were not detected due to inadequate sampling. In contrast, of 56 chondrosarcomas located in the metacarpal and metatarsal bones reported in literature,4,12,13,15,16,18,22,26,29,36-46 10 patients (18%) developed metastases (median follow-up of 3.1 years). In general, Grade 2 chondrosarcomas have a metastatic rate of 10–43%.6,47,48 This clearly demonstrates that phalangeal chondrosarcoma behaves differently from chondrosarcomas located elsewhere.

An explanation might be that these tumors are less malignant from a tumor biology point of view. We examined expression of the Ki-67 cell-cycle antigen, whose expression is associated closely with the proliferation phase of the cell, and the overexpression of p53, which occurs predominantly in high grade chondrosarcomas, suggesting a role for p53 in the progres-
sion of cartilaginous tumors. We found that the mean Ki-67 index in phalangeal chondrosarcoma is lower than in chondrosarcomas located elsewhere (Grade 2: P = 0.05). Although only of borderline statistical significance, this suggests that a lower proliferation rate may be associated with the more favorable behavior. Furthermore, the slightly lower number of p53 positive phalangeal chondrosarcomas might indicate that loss of p53 function may occur in an even later stage than in chondrosarcomas located elsewhere.

Another explanation could be that the phalangeal localization enables early detection. It is well documented that distal tumors are discovered at a significantly smaller size and therefore are more accessible for radical treatment and associated with a better prognosis. The median size (greatest dimension) in our series was 3 cm (range 1–8 cm) compared with 11 cm (femur) and 13 cm (pelvis) elsewhere (range, 2–32 cm). A median duration of symptoms of 18 months in the current study and 60 months in the literature compared with 6–16 months for chondrosarcomas in general would appear to contradict a favorable prognosis due to early intervention alone.

If we compare our data with a series of 110 enchondromas of the bones of the hand, we find that the average age of patients with phalangeal enchondroma is relatively low compared with phalangeal chondrosarcoma (35.4 years compared with 60.4 years). Both lesions are located predominantly in the proximal phalanx, which might suggest that phalangeal chondrosarcoma may arise from enchondroma. However, in only 5 cases in the current series (14%) and 18 cases in the literature (28%) could histologic or clinical evidence that phalangeal chondrosarcoma had arisen in a preexisting enchondroma be found. Because phalangeal enchondroma is relatively far more frequent compared with phalangeal chondrosarcoma, malignant transformation should be considered as a very rare phenomenon. This appears to indicate that when cortical destruction and soft tissue extension are absent and the histologic appraisal is benign, borderline or Grade 1 strictly according to the strict criteria of Evans et al. only pain or functional or cosmetic reasons should result in surgical intervention.

Because the metastatic rate in phalangeal chondrosarcoma is extremely low, one can even question the clinical usefulness of considering these tumors as chondrosarcomas, stigmatizing the patient as having cancer, versus a diagnosis of cellular enchondroma. However, the results of the current study show that phalangeal chondrosarcomas are characterized by their local destructive behavior. Of 110 enchondromas of the bones of the hand, only 5 tumors (4.5%) recurred due to inadequate curettage. Of 28 patients in the current study 10 (36%) developed a local recurrence, and 19 of 85 patients in the literature (22%) developed a local recurrence. We believe this finding would argue in favor of defining these lesions as chondrosarcoma versus cellular enchondroma, emphasizing the need for treatment and adequate follow-up.

The higher percentage of local recurrence in our series can be explained by the relatively lower percentage of radical surgery (54% vs. 75%) compared with the literature. It is known that the type of treatment significantly influences the recurrence rate and our data strongly support this finding. However, it should be noted that this is a multicenter study in which patients are treated by different surgeons. Furthermore, curettage of a phalangeal bone easily can lead to residual tumor tissue because bones are relatively small and cortical destruction is a prominent feature of phalangeal chondrosarcoma.

Phalangeal chondrosarcoma behaves as a locally aggressive lesion in which, in contrast to chondrosarcomas located elsewhere, metastatic disease is extremely uncommon. Histologically, phalangeal chondrosarcoma displays high grade histologic features combined with cortical destruction and soft tissue invasion. The tumor should be treated only because of its local aggressiveness. Although localized therapy and location in the proximal phalanx are associated strongly with local recurrence, we believe that, considering the excellent survival data, curettage with adequate follow-up can be justified in the first instance if technically feasible, especially in those cases in which amputation would lead to significant loss of function of the hand.

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