Cartilaginous Tumors of Bone: How to Distinguish Benign and Malignant

Eiichi Konishi, M.D., Ph.D.
Department of Pathology.
Kyoto Prefectural University of Medicine, Kyoto, Japan
Introduction

Chondrosarcoma (CHS) is a malignant tumor with pure hyaline cartilage differentiation\(^1\) which sometimes shows myxoid change, calcification and ossification\(^1\). WHO subclassifications (2002)\(^2\) are central, peripheral, dedifferentiated, mesenchymal and clear cell CHS \(^2\). Central CHS originates from the medullary cavity of the bones, and peripheral CHS is from their surface\(^3,4\). In contrast to primary, secondary CHS originates from the benign precursor lesions, such as enchondromas, osteochondromas, and dysplastic cartilaginous lesions of Maffucci’s syndrome and Ollier’s disease\(^1,5-12\). Most peripheral CHSs are secondary\(^1,6,13,14\). Conventional CHS is often used as a synonym for primary, central CHS. Mesenchymal\(^15-17\), clear cell\(^18,19\) and dedifferentiated\(^20,21,22\) CHS are special subtypes.

Conventional CHS usually occurs in the pelvic and long bones of middle-aged and older (>50 yo) individuals. It is the third commonest sarcoma among primary bone tumors after myeloma/lymphoma and osteosarcoma\(^1,13,14\). There is a slight male preponderance\(^23-27\). Small bones of the hands and feet are uncommonly involved. Radiological images can help in the diagnosis\(^6,28-32\).

Herein, the histopathology of conventional CHS is mainly discussed.
Histopathological criteria of chondrosarcoma

The histopathological criteria of CHS have long been discussed\textsuperscript{3, 23, 24, 26, 33-36}. The most accepted criteria, those of Lichtenstein and Jaffe (1943)\textsuperscript{3}, are as follows: 1) many cells with plump nuclei; 2) more than an occasional cell with two such nuclei; and 3) giant cartilage cells with large single or multiple nuclei, or with clumps of chromatin. CHS should be the diagnosis even if these features are present in only scattered areas of the viable non-calcified mass. In addition to their criteria, several features, such as cytological atypia, atypical mitoses, myxoid change, and permeative pattern, have been introduced\textsuperscript{23, 24, 26, 33-36}. In WHO blue book (2002)\textsuperscript{1}, cellular atypia, cellularity, binucleation, permeation, myxoid change, necrosis and mitosis are introduced as the features of CHS. When the lesions are in the small bones of the hands and feet, or at the periphery of bones, or secondary from such precursor lesions, as osteochondroma(tosis), Ollier’s disease, and Maffucci’s syndrome, distinct atypical features, which are usually seen in moderate grade (Grade 2) CHS, and/or invasiveness are required for diagnosis\textsuperscript{1,5, 7-12}. 


Differential diagnosis of conventional chondrosarcoma

Differential diagnoses of conventional CHS include chondroblastic osteosarcoma, chondromyxoid fibroma, chondroblastoma, and enchondroma.

a) Chondroblastic osteosarcoma (COS)\textsuperscript{37}

COS occurs in young patients (peak: 10-20 yo). COS often arises around the knee and at the metaphysis. COS is always high-grade malignancy and often presents destructive radiological images. Histologically, COS may contain neoplastic cartilaginous tissue, but it must have an area of spindle cell sarcoma, which is not present in conventional CHS.

b) \textsuperscript{38, 39}Chondromyxoid fibroma (CMF)\textsuperscript{38, 39}

CMF is an extremely rare tumor, often involving metaphyses of the long bones around the knee in young adults. CMF presents an eccentric lytic radiological image, which often reveals “scalloping” margin against the medulla. Sclerotic rim is common. Lobular arrangement of myxoid matrix with small spindle or stellate cells is noted, with a rim of “fibrous” area, containing osteoclast-type giant cells. Conventional CHS does not have a “fibrous” area.

c) Chondroblastoma (CB)\textsuperscript{40, 41}

CB is a rare tumor involving epiphysis or epimetaphysis of the long bone. Radiologically, a distinct lytic lesion with occasional calcification is seen. Histologically, immature pink chondroid matrix and diffuse mononuclear tumor cell proliferation are characteristics. It is usually easy to differentiate CB from conventional CHS.

d) Enchondroma(ECH)\textsuperscript{5, 42}

ECH often affects the small bones of the hands and feet, but may affect the long
bones. It may occur at any age. Radiologically, a well bordered calcified or lytic mass is found in the medullary cavity. Cortical thickening and marked erosion of the cortex are uncommon in ECH of the long bones. Histologically, a hypocellular hyaline cartilaginous tumor shows variable calcification. Cellular atypia is not present, except in small bones, where ECH may show cellular atypia, and rather high cellularity and have myxoid matrix.

Ollier’s disease and Maffucci’s syndrome show multiple chondromas at any portion of the skeleton that are thought to be dysplastic lesions. They may affect the periosteum. The cartilaginous lesions may reveal high cellularity, myxoid change of the matrix, and cellular atypia. In Maffucci’s syndrome, soft tissue hemangioma is also noted. It is difficult to differentiate these cartilaginous lesions from CHS without clinical and radiological findings.
Low-grade (Grade 1) chondrosarcoma vs. enchondroma in long bones

Differential diagnosis between low-grade (Grade 1) conventional CHS and enchondroma (ECH) in the long bones is still challenging. As mentioned above, in addition to the criteria of Lichtenstein and Jaffe, several histological features, such as atypical mitoses, myxoid change, cellular atypia, invasiveness (permeation), cell necrosis, multiple chondrocytes in a single lacuna, and periosteal reaction, have been introduced for more precise differentiation between Grade 1 (G1) CHS and ECH.

Because individual specialists in bone pathology use their own diagnostic criteria for CHS, reproducibility and reliability of each diagnosis are questionable. Eefting et al. tried to find the reproducible and statistically significant histologic features that could differentiate central G1 CHS from ECH. They noted that in histology, entrapment, nuclear pleomorphism, cellularity and irregular distribution of cells were statistically significant in univariate analyses and showed high positive predictive value for CHS. In multiple stepwise logistic regression method, histological parameters (cellularity, entrapment, open chromatin and mucoid matrix) and a clinical parameter (age above 45 years) were the most predictive combination to differentiate central G1 CHS from ECH. Especially, mucoid change (≥20%) and entrapment were introduced as the significant features, which were easy to use for differential diagnosis between G1 CHS and ECH with good sensitivity and specificity. These two, especially the latter, are the features of invasive (permeative) nature. The invasiveness has been noted as the most important characteristic of low-grade CHS in the previous literatures.

In addition to histological findings, clinical and radiological findings can help the differentiation. Pain in history and cortical irregularity in radiology, such as thickening and scalloping, are considered as signs for CHS, but they do not have high specificity.
The radiological criteria have the same problems in reproducibility and reliability as pathological ones.

In order to elucidate the objective criteria for CHS, molecular and genetic analyses as well as cytometry have been performed. Although some abnormalities, such as aneuploidy, aberrancy of chromosome 1 and 7, Ki-67 index, abnormalities of p53 and 13q, LOH on 10q, and abnormalities of CDK family (e.g., p16\textsuperscript{INK4a}, p15\textsuperscript{INK4b}), are considered to be clinically significant, the critical abnormality which can differentiate CHS from ECH has not yet been found.
Grading of chondrosarcoma

CHS other than special subtypes should be graded histologically (Grade 1, 2, 3 = low, moderate, high) because there is a prognostic significance of histological grading\(^1,4\), 25, 27, 28, 34, 46, 55. Several grading systems have been developed\(^4, 23, 26, 27, 34, 46, 56, 57\). Essentially, nuclear size, hyperchromasia and cellularity are the histological parameters for grading\(^1\). Other features, such as necrosis, mitotic figures, and bi- or multi-nucleated cells, are also employed. WHO blue book (2002)\(^1\) introduces the following: Grade 1: moderate cellularity, uniform plump nuclei with hyperchromasia, occasional binucleated cell; Grade 2: more cellular, more nuclear atypia, more hyperchromasia and larger nuclear size; Grade 3: more cellular, pleomorphic and atypical, mitotic figures which are easily found.

Based on various types of grading system, Grade 1(G1) comprises 40-60%, Grade 2(G2) 30-50%, and Grade 3(G3) 6-25%\(^23,27,46\). When the locations are limited to the long tubular bones and the bones of limb girdles, G1:G2:G3 is 60.9%:35.3%:3.2%\(^28\). The five-year survival rates for G1 to G3 CHS are 90%, 81%, and 43%\(^27\), and the ten-year rates are 77-83%, 59-64%, and 29-36%\(^25,27\). Metastatic disease and local recurrence are often seen in high-grade CHS, especially G3, and the lung is the most common site of metastasis\(^25, 27, 46\). Grading is the single most important predictive factor of local recurrence and metastasis in multivariate analysis\(^28\).

The grading is also very important because G1 CHSs are often curedtted with adjuvant therapy (e.g., phenol, cryosurgery) while G2 CHSs are not\(^58-60\).
Is it possible to differentiate low-grade (Grade 1) chondrosarcoma in long bones from enchondroma by only histological findings?

This has been a controversial subject. While it is very important to know the pathological features that can differentiate CHS from ECH, pathologists need to know that CHS is heterogeneous in histology. Due to the heterogeneity, some CHSs were overlooked. In our experience, the histological grade of the surgical material is often higher than that of the biopsy specimen (29/73 cases, 39%), and entrapment, which is thought to be the most important features of malignancy, is present in only 29% of preoperative biopsy specimens (22 of 75 cases). To avoid false negatives, it is very important to obtain abundant material from appropriate location for biopsy as well as to obtain clinical and radiological findings. When diagnosing the curetted materials, which are frequently used for treatment of ECH and low-grade (G1) CHS in the long bones, there is a diagnostic difficulty due to fragmentation of the specimens. One may overestimate invasive features such as entrapment.

It is still true that pathologists rely on the great help of orthopedic surgeons and radiologists, as noted by Jaffe (“Jaffe’s triangle”), especially when diagnosing cartilaginous tumors.
Conclusion

1. Histological criteria for chondrosarcoma (CHS) are generally based on the criteria of Lichtenstein and Jaffe (1943), evaluating nuclear size, number of nuclei, and giant cells with clumped chromatin. Additional features, such as myxoid change, invasiveness, cellularity, necrosis and mitosis, are also used.

2. When the lesions are in the small bones of the hands and feet, at the surface of the bone, or secondary to the precursor cartilaginous lesions, the criteria for diagnosis are more stringent. Distinct atypical features as Grade 2 or more and/or invasiveness are needed for diagnosis as CHS.

3. Histological differential diagnosis between Grade 1 CHS and enchondroma (ECH) is always challenging, especially in the long bones. The most significant histological parameter for differential diagnosis is invasive nature (e.g., entrapment).

4. CHS is heterogeneous in histology. To avoid false-negatives, several biopsies from the optimal location are necessary.

5. Grading for CHS is mandatory, not only because of the prognostic significance, but also because the operational method may be changed according to grade.

6. Without clinical and radiological findings, it is still difficult to differentiate G1 CHS from ECH. The importance of collaboration among pathologists, radiologists and orthopedic surgeons (Jaffe’s triangle) remains unchanged.
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Cartilaginous Tumors of Bone: How to Distinguish Benign and Malignant

Eiichi Konishi, M.D., Ph.D.
Department of Pathology, Kyoto Prefectural University of Medicine, Kyoto, Japan
Chondrosarcoma (CHS)

- **Definition** (WHO, 2002)
  - A malignant tumor with pure hyaline cartilage
  - May have myxoid area, calcification, and/or ossification
Classification (WHO, 2002)

- Central, primary, and secondary
- Peripheral
- Dedifferentiated
- Mesenchymal
- Clear cell
- Central (intramedullary origin)
  - Primary
    - No precursor lesion
    - Common
      - Conventional chondrosarcoma
  - Secondary
    - Arising from enchondroma(tosis)
    - Rare
      - Ollier’s disease, Maffucci’s syndrome
• Peripheral (Surface origin)
  – Primary
    • Periosteal chondrosarcoma
    • Extremely rare
      – Usually distal femur, metaphysis

  – Secondary
    • Arising from osteochondroma(tosis)
    • More often than periosteal CHS
      – Often in the limb girdles
• Special subtype
  • Dedifferentiated
    • High-grade spindle cell/pleomorphic sarcoma in low-grade CHS
  • Abrupt transition
• Mesenchymal
  • Small round cell sarcoma with chondroid matrix
  • Occurs in both bone and soft tissue
• Special subtype (continued)

• Clear cell
  • Epiphysis of the long bone
  • Osteoid formation
  • Clear tumor cells
  • Moderate grade
  • Area of conventional CHS
Differential diagnosis of CHS

- **Central**
  - enchondroma, chondromyxoid fibroma, chondroblastoma, chondroblastic osteosarcoma

- **Peripheral**
  - periosteal chondroma, osteochondroma
It is always challenging for pathologists to make a differential diagnosis of CHS, especially in the long bones.

What is the key for differential diagnosis?
Case

- A 57-year-old male.
- He had felt a pain at his left hip since five months previously.
Radiology
Radiological findings

- A lytic lesion with some dot-like calcification
- Scalloping of the cortex
- Some cortical thickening at the distal site

Radiological diagnosis:
Highly suggestive of chondrosarcoma
Needle biopsy
Pathological findings of the biopsy

- Hypocellular
- Myxoid matrix
- Mild cellular atypia
- Only a few preexisting non-neoplastic bone trabeculae were included.

Diagnosis:
Low-grade (Grade 1) chondrosarcoma
Macroscopic view of the surgical material

- transparent nodules
- cortical irregularities
- No soft tissue mass
Histology of the surgical material
Pathological findings of the surgical specimen

- Hypocellular
- Myxoid change
- Mild cellular atypia

- Obvious invasiveness
  - Cortical erosion, entrapment

- Diagnosis
  - Low-grade (Grade 1) chondrosarcoma
Summary of the case

- Middle-aged man
- Pain
- Proximal femur, metaphysis
- Intramedullary lesion
- Solitary lytic mass with some calcification
- Cortical irregularities
- Hypocellular tumor with myxoid matrix
- Mild cellular atypia
- Invasive (permeative) pattern
Differential diagnosis

- chondroblastic osteosarcoma
- chondroblastoma
- chondromyxoid fibroma
- enchondroma
• Chondroblastic osteosarcoma (COS)
  – 2\textsuperscript{nd} decade (10-20 yo)
  – around knee
  – destructive radiological images
  – spindle cell sarcoma with chondroid matrix
• Chondroblastoma (CB)
  – young age
  – epiphysis or epimetaphysis of the long bone
  – diffuse mononuclear cell proliferation
  – immature pink chondroid matrix
  – chicken wire calcification
Chondromyxoid fibroma (CMF)

- young adults
- around knee, metaphysis
- eccentric lytic mass
- scalloping against medulla
- myxoid lobules with mononuclear tumor cells
- fibrous area with osteoclast-type giant cells
**Enchondroma (ECH)**

- any age
- often in small bones of the hands and feet
- may occur in the long bones

a. **Long bones**

- calcified mass
- no cortical irregularity
- lobules of hyaline cartilage
- hypocellular
- no cellular atypia
b. Small bones of the hands and feet

- lytic mass with or without calcification
- cortical thinning
- pathological fracture
- may show
  - myxoid change
  - Moderate cellularity
  - Mild cellular atypia
- no soft tissue mass
Summary of the case

- Middle-aged man
- Pain
- Proximal femur, metaphysis
- Intramedullary lesion
- Lytic mass with some calcification
- Cortical irregularities
- Hypocellular tumor with myxoid matrix
- Mild cellular atypia
- Invasive (permeative) pattern
Diagnosis of the case

- Low-grade (Grade 1) chondrosarcoma

  • May not be so difficult to diagnose this case.
Histological continuity between low-grade chondrosarcoma and enchondroma
What is the key for differential diagnosis?
The histological criteria for CHS

- Historical review (1)
  - 1925: Keiller, VH
    - cytologic features (particularly nucleus)
    - atypical mitosis
    - not myxoid change
  - 1943: Lichtenstein, L & Jaffe, HL
    - mainly cytologic features
1943: Lichtenstein, L & Jaffe, HL
Even in scattered area
(in viable noncalcified mass)

1) Many cells with plump nuclei
2) More than an occasional cell with two such nuclei
3) Giant cartilage cells with large single or multiple nuclei or with clumps of chromatin

no myxoid change
**Historical review (3)**

1951: O’Neal LV & Ackerman LV follow the criteria of Lichtenstein & Jaffe (L&J) periosteal reaction (ECH vs. low-grade CHS) myxoid change – no meaning

<table>
<thead>
<tr>
<th>Histological features</th>
<th>enchondroma</th>
<th>chondrosarcoma(low-grade)</th>
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<tbody>
<tr>
<td>Variation in nuclear size</td>
<td>Little or none in long bones; may vary in hands and feet; small nuclei</td>
<td>Occasional very plump nucleus; general plumping of many nuclei</td>
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<tr>
<td>Double nuclei</td>
<td>Rare and not plump</td>
<td>Low incidence; may be plump</td>
</tr>
<tr>
<td>Multinucleated giant cells</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Calcification</td>
<td>Frequent</td>
<td>Frequent</td>
</tr>
</tbody>
</table>
• Historical review (4)

• 1956: Dahlin DC, Henderson ED follow the criteria of L&J.

  - myxoid change (worrisome sign)
  - generous biopsy (heterogeneity)

• 1980: Sanerkin NG.
  - invasiveness (important)
  - (low-grade CHS vs. ECH)
  - cytologic atypia
• Historical review (5)

• 1985: Schiller, AL
  G1 CHS vs. ECH

G1 CHS:
confluent lobules, myxoid matrix, cell necrosis, entrapment, soft tissue extension, prominent chromatin and nucleoli, pleomorphic and hyperchromatic nuclei, multiple chondrocytes in a single lacuna, multinucleated cells

ECH: pink rim in lobule, reactive bone outlining each lobule, map-like dense calcification
• Historical review(6)

1985: Mirra JM, et al. Cytologic findings (e.g., L&J criteria) may overlap between G1 CHS and ECH.

- Enchondromatous pattern
- Island of cartilage pattern
- Encasement pattern

- Chondrosarcomatous pattern (1)
- Permeation pattern (only one important)
- Entrapment
  (regardless of cellular atypia)
Entrapment
1985: Mirra JM, et al. (continued)

Chondrosarcomatous pattern (2)
cortical invasion, soft tissue mass,
marrow fat, invasion, bands of fibrosis

Curettage material --- so fragmental
may be mistaken for permeative pattern.

Heterogeneity (preexisting ECH)

Pain
• Historical review (8)

• 1998: Björnsson J et al. only definitive histological criterion
  --- permeation

• 2002: WHO blue book
  cellularity, cellular atypia, binucleation, permeation (important), myxoid change, necrosis
  mitosis (high-grade lesion)
Typical features of CHS
Important rule for the application of the criteria

- Different in locations
  - central or peripheral?

- Different in bones
  - small bones of hands and feet or large bones?

- Different between primary and secondary lesion
Different application of the criteria

- **Peripheral CHS**
  - *Periosteal chondrosarcoma*

- **Central CHS**
  - *Small bones of the hands and feet*

- **Secondary CHS**
  - Central
    - Secondary to enchondromatosis
      - *Ollier’s disease and Maffucci’s syndrome*
  - Peripheral
    - Secondary to osteochondromatosis
Different application of the criteria

• The criteria are more stringent.
  – Distinct atypical features
    • Usually seen in moderate grade (G2) CHS in other bones or locations.

  – Obvious invasiveness
    • Soft tissue mass (central CHS)
    • Intramedullary and/or soft tissue invasion (peripheral CHS)
Histological criteria between CHS and ECH --- objective or subjective?

- 2007: Skeletal Lesions Interobserver Correlation among Expert Diagnosticians (SLICED) Study Group

Using cartilaginous tumors in long bones (ECH, G1, G2, and G3 CHSs)

The reliability and reproducibility of diagnosis of cartilaginous tumor.

-----questionable!!!

κ coefficient = 0.443 (pathologists)

= 0.345 (radiologists)
2009: Eefting, D et al.

18 specialists, CHS and ECH (central lesion) 
$\kappa$ coefficient=0.78, in cartilaginous tumors 
$\kappa$ coefficient=0.54, in G1 CHS vs. ECH

Optimal histological features to differentiate central G1 CHS from ECH? (multivariate analysis)

Cellularity, entrapment, open chromatin, mucoid matrix, age (>45 yo)
Most reliable and convenient criteria
G1 CHS vs. ECH
Mucoid matrix $\geq 20\%$ and/or entrapment
(sensitivity and specificity: 95%)

Especially entrapment is the feature of invasiveness (permeation).
Question!

- Is it possible to differentiate low-grade (G1) CHS from ECH in the long bones, based on only pathological findings?

We compare G1 CHS and ECH in the long bones.
CHS in Kansai area, JAPAN

21 million (population)

Osaka
Kyoto
Kobe
CHS in Kansai area, JAPAN

- 14 hospitals in Kansai area
  - Kyoto University, Kyoto Prefectural University of Medicine, Kyoto 1st and 2nd Red Cross Hospitals, Saiseikai Kyoto Hospital
  - Otsu Municipal Hospital
  - Osaka University, Osaka City University, Osaka National Hospital, Osaka Medical Center for Cancer and Cardiovascular Disease, Osaka City General Hospital, Matsushita Memorial Hospital
  - Hyogo College of Medicine, Hyogo Cancer Center

- 201 cases (primary and secondary)
- Almost all were operated.
CHS in Kansai area, JAPAN

- Primary: 180 cases
- Secondary: 21 cases
- M:F=99:102
- Age: 48.8 (average), 51.0 (median)
- Follow up:
  - 64 months (average)
  - 48 months (median)
Primary & Secondary

total: 201 cases

- Skull: 2
- Scapula: 12
- Humerus, proximal: 40
- Humerus, unknown: 3
- Humerus, mid: 4
- Radius, distal: 1
- Finger: 3
- Femur, proximal: 22
- Femur, mid: 2
- Femur, unknown: 2
- Femur, distal: 24
- Tibia, proximal: 9
- Tibia, mid: 2
- Tibia, distal: 1
- Fibula, proximal: 3
- Tarsal: 1
- Toe: 3

2012/2/1
Primary

total: 180 cases

- Skull: 2
- Scapula: 8
- Humerus, proximal: 39
- Humerus, unknown: 3
- Humerus, mid: 4
- Radius, distal: 1
- Finger: 3
- Femur, proximal: 20
- Femur, mid: 2
- Femur, unknown: 1
- Femur, distal: 24
- Tibia, proximal: 6
- Tibia, mid: 2
- Fibula, proximal: 3
- Tarsal: 1
- Toe: 2
Pathological features used for comparison between G1 CHS and ECH in the long bones

- Number of the nuclei in multinucleated cells (≤2, >2)
- Pleomorphism (0~4+)
- Pyknosis of the nucleus (+, -, ?)
- Pale chromatin (+, -)
- Mitotic figure (+, -)
- Arrangement of the tumor cells in the lobule (regular, irregular)
- Cellularity (1+~5+)

(to be continued)
• Secondary ossification (+, -)
• Calcification (+, -)
• Encasement (+, -, ?)
• Entrapment (+, -, ?)
• Cortical invasion (+, -, ?)
• Density of chromatin (0~4+)
• Number of mitotic figures (0, 1-2/10HPF, >2/10HPF)
• Hyaline chondroid matrix (0~3+)
• Myxoid matrix (0~3+)
• Cell necrosis (0~3+)
Grade 1 primary chondrosarcoma of the long bones:
- 69 cases
- average 49.7 yo
- humerus(35), femur(29), tibia(3), fibula(2)

Enchondroma (solitary) of the long bones:
- 17 cases
- average 44.9 yo
- humerus(12), tibia&femur(2 each), fibula(1)
Analysis between G1 CHS and ECH in long bones

- **Statistical significance (p<0.05)** in univariate analysis
  - Pleomorphism (0 and 1+~4+)
  - Density of chromatin (0 and 1+~4+)
  - Hyaline chondroid matrix (0~1+ and 2+~3+)
  - Myxoid matrix (0~1+ and 2+~3+)
  - Necrosis (0~1+ and 2+~3+)
  - Entrapment (- and +)
G1 CHS vs. ECH in long bones

- Statistical significance (p<0.05) in multivariate analysis (multiple logistic regression analysis)
  - Myxoid matrix (0~1+ and 2+~3+)
  - Entrapment (+, -)
  - Density of chromatin (0 and 1+~4+)
Clinical features?

- **age (p=0.23)**
  - ECH(average: 44.8 yo)
  - G1 CHS(average: 49.7 yo)

- **pain (p=0.09)**
  - ECH(5/16 cases)
  - G1 CHS(14/24 cases)
Comparison with the previous literatures
G1 CHS vs. ECH

- Eefting D. et al.
  - significant and convenient criteria for CHS by multivariate analysis
    (central, all bones)
    mucoid matrix ≥20% and/or entrapment
    (sensitivity 95%, specificity 95%)

- Sanerkin NG., Mirra JM. et al., Schiller AL, Björnsson J. et al., Bertoni F. et al., Unni KK. et al.
  - Most important feature of G1 CHS is invasiveness (permeation).
Our result (primary, central, long bones)
- myxoid matrix (0~1+ and 2+~3+)
- entrapment (+, -)
- density of chromatin (0 and 1+~4+)
  (p<0.05, in multivariate analysis)

Sensitivity: 92%, Specificity: 76.5%

Our result (primary, central, all bones)
in addition to the above listed features
- age (>50 and ≤50)
- calcification (+, -)
  (p<0.05, in multivariate analysis)
Differential diagnosis between G1 CHS vs. ECH

Invasiveness (permeation) is the most important histological feature for differential diagnosis.
Heterogeneity in histology of CHS

- 1957: Dahlin DC
  - CHS has heterogeneity in histological grade.

- 1983: Mirra JM et al.
  - Coexistence of ECH and G1 CHS (secondary to ECH?)
In our study

- CHSs were often diagnosed as higher grade in the surgical material than in the biopsy (29/74 cases, 39%)

- Entrapment was present in only 27% of the biopsy of CHS (20/74 cases).
Is it possible to differentiate low-grade (G1) CHS from ECH in the long bones, based on only pathological findings?

Answer:
It may be possible based on only pathological findings, but heterogeneity is a big problem.
• To avoid false-negatives, as the previous literature noted (Dahlin, Mirra, etc.)

Need to obtain adequate biopsy material from appropriate site.

Need clinical and radiological guidance!!
Clinical and radiological findings

- Age, Sex
- Location
  - long bone?, small bone?
  - surface or intramedullary?
- Precursor lesion?
  - osteochondroma?
- Solitary or multiple?
  - Maffucci’s syndrome
  - Ollier’s disease
• Radiological images
  – Number of lesions?
  – Location?
  – Invasiveness?
    • cortical irregularities
    • destruction
  – Matrix (MRI, CT)
    • calcified?
    • myxoid?
  – Soft tissue mass? (MRI, CT)
  – Dedifferentiation? (MRI, CT)
Jaffe’s triangle (1958)

Orthopedic Surgeon

Radiologist

Pathologist

Be a good team!!

Accurate Diagnosis and Good Therapy!!

Importance still unchanged
Grading of CHS

- Once you diagnose a CHS (except special subtype), you need to grade the lesion.
Why do we need to grade CHS?

- Prognostic significance
  - Local recurrence
    - high incidence in high-grade CHS
  - Metastasis (usually lungs)
    - high incidence in high-grade CHS
  - Survival rate
    - low in high-grade CHS
Grading of CHS

Grading based on

- cytologic appearance
  -- nuclear size
  -- hyperchromasiasia
- cellularity

(WHO, 2002)
Grading by WHO criteria (2002)

- Grade 1: moderate cellularity, uniform plump nuclei with hyperchromasia, occasional binucleated cell

- Grade 2: more cellular, more nuclear atypia, more hyperchromasia and larger nuclear size

- Grade 3: more cellular, pleomorphic and atypical, mitotic figures which are easily found.
Grade 1 CHS
Grade 1 CHS
Grade 2 CHS
Grade 2 CHS
Grade 2 CHS
Grade 3 CHS
Grading of CHS

- Historical review (1)

- 1952: O’Neal LW, Ackerman LV
  based on the criteria of Lichtenstein & Jaffe

Low, moderate, high
  nuclear size
  binuclear cell
  multinucleated
  giant cell, calcification
### Historical review (2)

**1952:** O’Neal LW, Ackerman LV

<table>
<thead>
<tr>
<th>Histological features</th>
<th>Enchondroma</th>
<th>Chondrosarcoma Low-grade</th>
<th>Chondrosarcoma Moderately Malignant</th>
<th>Chondrosarcoma Highly Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variation in nuclear size</td>
<td>Little or none in long bones; may vary in hands and feet; small nuclei</td>
<td>Occasional very plump nucleus; general plumping of many nuclei</td>
<td>Frequent very plump nuclei; general plumping of many nuclei</td>
<td>Great variation; large numbers of very plump nuclei</td>
</tr>
<tr>
<td>Double nuclei</td>
<td>Rare and not plump</td>
<td>Low incidence; may be plump</td>
<td>Frequent plump double nuclei</td>
<td>Very many</td>
</tr>
<tr>
<td>Multinucleated giant cells</td>
<td>None</td>
<td>None</td>
<td>None to rare</td>
<td>Occasional to frequent</td>
</tr>
<tr>
<td>Calcification</td>
<td>Frequent</td>
<td>Frequent</td>
<td>Occasional but to slight degree</td>
<td>None</td>
</tr>
</tbody>
</table>
• Historical review (3)

• 1956: Dahlin DC, Henderson ED
  Grading based on cytologic appearance
  nuclear pleomorphism,
  hyperchromasia,
  multinucleated giant cells

212 cases (G1:G2:G3 = 54.7%:37.3%:6.1%)
• Historical review (4)

1977: Evans, HL, Ayala, AG, Romsdahl, MM

71 cases (G1:G2:G3 = 45%:30%:25%)
Grading by
mitotic rate, cellularity, nuclear size

5-year survival G1, G2, G3
= 90%:81%:43%

10-year survival G1, G2, G3
= 83%:64%:29%

Metastasis G2, G2, G3
= 0%:10%:71%
1977: Grading criteria by Evans, HL, et al.

Grade 1:
- small and dark-staining nuclei,
- chondroid to myxoid background
- frequent calcification and/or bone formation
- 2 or more nuclei in a lacuna
- local aggressiveness

Grade 2:
- moderate size nucleus, low mitotic rate (<2/10HPF)
- cellularity increasing at the periphery of the lobule
- visible intranuclear detail
- myxoid > chondroid
- heterogeneity

Grade 3:
- mitotic rate (2≤/10HPF),
- greatest cellularity at the periphery
- spindle cell sarcoma at the periphery
  (no matrix)
Historical review(5)

1980: Prichard DJ et al.
280 cases (G1:G2:G3=57%:34%:9%)

Grading with Evans’s criteria

limbs, limb girdles, spinal column

10-year survival  G1:G2:G3
=77%:59%:36%
• **Historical review(6)**

• **1998: Björnsson J et al.**
  primary, limbs, limb girdles
  344 cases(G1:G2:G3=60.9%:35.3%:3.2%)
  by cellularity, nuclear size, hyperchromasia

  **Grading is the single most important predictive factor of local recurrence and metastasis.**

• **1999: Lee FY et al.**
  227 cases (G1:G2:G3=31%:62%:17%)
  by cellularity, character of the cells, matrix, replicative activity
  high grade (G2&G3)
  metastasis, local recurrence, death
Grading of CHS

- Grading is very important.
  - G1 CHS
    Curettage with adjuvant therapy, such as phenol, cryosurgery and ethanol.
  
  - G2 and G3 CHS
    Resection
CHS in Kansai area, JAPAN

Grade

Primary: 180 cases, Secondary: 21 cases
Total: 201 cases

- Grade 1: 101 (50.2%)
- Grade 2: 80 (39.8%)
- Grade 3: 20 (10%)

all bones

Classified by the criteria, based on WHO blue book (2002)
Overall survival, all bones

Grade 1

Grade 2

Grade 3

G1 vs. G2: p<0.002
G2 vs. G3: p<0.0004
G1 vs. G3: p=6.38E-12
CHS in Kansai area, JAPAN
Grade

primary and secondary, all bones

- 5-year survival
  - G1:G2:G3=98%:86%:36%

- 10-year survival
  - G1:G2:G3=94%:74%:36%

G1 vs. G2: p<0.002
G2 vs. G3: p<0.0004
G1 vs. G3: p=6.38E-12
Overall survival, all bones, primary

Grade 1

Grade 2

Grade 3

G1 vs. G2: p<0.005
G2 vs. G3: p<0.003
G1 vs. G3: p<7E-09

Survival period

months
CHS in Kansai area, JAPAN
Grade

primary, all bones

• 5-year survival
  – G1:G2:G3=96%:85%:38%

• 10-year survival
  – G1:G2:G3=92%:73%:38%

G1 vs. G2: p<0.005
G2 vs. G3: p<0.003
G1 vs. G3: p<7E-09
Overall survival, primary, long bones, Grade 1, wide resection vs. curettage

WR vs. C: p=0.49
WR=48 cases
C=21 cases
Conclusion 1

- Histological criteria for CHS are generally based on the criteria of Lichtenstein and Jaffe (1943), evaluating nuclear size, number of nuclei, and giant cells with clumped chromatin.

- Additional features, such as myxoid change, invasiveness, cellularity, necrosis and mitosis are also used.
Conclusion 2

• When the lesions are in the small bones of the hands and feet, at the surface of the bone, or secondary to the precursor cartilaginous lesions, the criteria for diagnosis are more stringent.

• Distinct atypical features as G2 or more and/or invasiveness are needed for diagnosis as CHS.
Conclusion 3

- Histological differential diagnosis between G1 CHS and ECH is always challenging, especially within the long bones.

- The single most significant histological parameter for differential diagnosis is that for invasive nature (e.g., entrapment).
Conclusion 4

- CHS is heterogeneous in histology.
- To avoid false-negatives, several biopsies from the optimal location are necessary.
Conclusion 5

- Grading for CHS is necessary, not only because of the prognostic significance, but because the operational method may be changed due to grade.
Conclusion 6

- Without reliance on clinical and radiological findings, it is still difficult to differentiate G1 CHS from ECH.

- The importance of collaboration among pathologists, radiologists and orthopedic surgeons (Jaffe’s triangle) remains unchanged.
Acknowledgments

- Nakashima Y.
  - Kyoto University

- Nakayama T., Toguchida J.
  - Kyoto University

- Murata H.
  - Kyoto Prefectural University of Medicine, Matsushita Memorial Hospital

- Ueda H.
  - Kyoto 1st Red Cross Hospital

- Katsura K.
  - Kyoto 2nd Red Cross Hospital

- Takeshita H.
  - Otsu Municipal Hospital

- Yoshikawa H.
  - Osaka University

- Hoshi M., Wakasa K.
  - Osaka City University

- Ueda T., Mano M.
  - Osaka National Hospital

- Araki N., Tomita Y.
  - Osaka Medical Center for Cancer and Cardiovascular Disease

- Inoue T., Aono M.
  - Osaka City General Hospital

- Kawabata K.
  - Matsushita Memorial Hospital

- Sakuma T.
  - Hyogo Cancer Center

- Tsukamoto Y., Futani H.
  - Hyogo College of Medicine

- Yano K.