

## Tumor grade-related thallium-201 uptake in chondrosarcomas

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### Abstract

**Objectives** Diagnosis of low-grade chondrosarcoma, especially discrimination between enchondroma and low-grade chondrosarcoma, may be difficult pathologically. The aim of this study was to evaluate the value of thallium-201 (Tl-201) scintigraphy in the diagnosis of chondrosarcoma and to investigate whether there was a correlation between Tl-201 uptake and tumor grade.

**Methods** We retrospectively evaluated 121 patients with pathologically proven bone and soft tissue tumors diagnosed between the years 1999 and 2007. All patients were followed by the Bone and Soft Tissue Tumor Working Group in our hospital. Twenty-three patients, mean age  $44 \pm 15$  (range 17–72) years, with a diagnosis of cartilaginous tumors were included. Increased Tl-201 uptake at the lesion sites greater than background was evaluated as malignant tumor. For the pathologic classification, a grading system (grade 1–3) based on the histopathologic findings was used. Pearson correlation coefficient was used

to determine whether there was any correlation between Tl-201 uptake and tumor grade in chondrosarcoma.

**Results** There were 7 enchondromas and 16 chondrosarcomas. Four of 16 patients with chondrosarcoma had lesions pathologically classified as grade 3, 5 as grade 2, and 7 had grade 1 chondrosarcoma. Increased Tl-201 uptake was observed in all patients with grade 3 chondrosarcoma and 2 patients with grade 2 chondrosarcoma. Of 10 patients with chondrosarcoma, 3 grade 2 chondrosarcomas and 7 grade 1 chondrosarcomas, there was no Tl-201 uptake in the tumor region. A significant correlation was found between Tl-201 uptake and tumor grade in chondrosarcoma ( $p = 0.002$ ,  $r = 0.71$ ). Only a few reports in literature have demonstrated false negative results in low-grade chondrosarcoma.

**Conclusion** Tl-201 uptake was related to tumor grade in chondrosarcoma. If there is a possibility of chondrosarcoma, Tl-201 scintigraphy should be reported with caution.

**Keywords** Tl-201 · Chondrosarcoma · Tumor grade

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### Introduction

Cartilaginous tumors, which include both benign and malign lesions, are one of the most common neoplasms of bone and soft tissue [1]. Diagnosis and histological classification of cartilaginous tumors, especially chondrosarcoma, require considerable specific experience and are not reliable if clinical and anatomic–radiographic data are not taken into account [2]. Grading system (grade 1–3) is important in predicting biologic behavior and prognosis. When first diagnosed, two-thirds of chondrosarcoma are low grade. Diagnosis of low-grade chondrosarcoma, especially the discrimination between enchondroma and

low-grade chondrosarcoma may be difficult pathologically. Pathologists need some information, such as radiologic findings or tumor vascularity and tumor appearance, during surgery. For the therapy aspect, the vast majority of enchondromas do not require a biopsy or surgical treatment. If the clinico-imaging setting and biopsy indicate a low-grade chondrosarcoma, the lesion should be accordingly treated with wide resection [2].

The prognosis of chondrosarcoma essentially depends on 2 factors: the possibility of wide excision and the histological grade of malignancy. The risk of metastasis is also highly dependent on tumor histology and grade [3–5]. In this area, imaging methods could play an important role in terms of evaluation of the grade of malignancy.

Thallium-201 (Tl-201) chloride, a monovalent cationic agent with biological properties similar to those of potassium, has become a useful agent for various neoplastic processes such as thyroid, brain, breast, lung and bone and soft tissue sarcomas [6]. The tumor uptake of Tl-201 depends on tumor size, viability, vascularity, cellularity and the histologic type of tumor [7].

Tl-201 has been used in staging, restaging and response to therapy of patients with bone and soft tissue tumors [8–10]. The correlation between histological degree of tumor necrosis and changes in Tl-201 uptake in patients with bone tumors has been investigated to predict the response to preoperative chemotherapy [8, 10]. Only a few reports in literature have focused on Tl-201 uptake in cartilaginous tumors. Tumor grade-related Tl-201 uptake in chondrosarcoma was proposed in 1 case report. The aim of this study was to evaluate the value of Tl-201 scintigraphy in the diagnosis of chondrosarcoma and to determine whether a correlation exists between Tl-201 uptake in cartilaginous tumors and tumor grade.

## Materials and methods

### Subjects and study protocol

We retrospectively evaluated 121 patients with pathologically proven bone and soft tissue tumors diagnosed between the years 1999 and 2007. All patients had newly diagnosed, untreated benign or malignant lesions. They were followed by the Bone and Soft Tissue Tumors Working Group in our hospital. Twenty-three patients, mean age  $44 \pm 15$  (range 17–72) years, with the diagnosis of chondrogenic tumors were included in this study. Radiography, CT or MRI imaging, bone scintigraphy and Tl-201 scintigraphy were available for review in all patients.

### Imaging procedure

For Tl-201 scintigraphy, a 3-mCi dose of Tl-201 was administered intravenously. Twenty minutes and 2 h after the injection, anterior and posterior whole-body imaging was performed, and 10-min anterior, posterior and, if necessary, lateral static images of the region of interest were acquired. The images were evaluated visually. Because chondrosarcoma shows lower Tl-201 uptake than osteosarcoma, increased uptake in early and late images greater than background activity on Tl-201 scintigraphy was evaluated as malignant tumor. A scoring system was used during the evaluation of early and late Tl-201 images. On either early or late images, no uptake or normal uptake in the tumor region was evaluated as 1, while increased uptake more than background activity was evaluated as 2.

### Pathology

For the pathologic classification of chondrosarcoma, cellularity, nuclear pleomorphism, binucleated cells, mitotic figures and necrosis were examined. Chondrosarcoma was separated into 3 histological grades: low (grade 1), medium (grade 2) and high (grade 3). Grade 1 chondrosarcoma was moderately cellular and contained small, hyperchromatic nuclei, which were occasionally binucleated. Mitotic figures and necrosis were not observed in grade 1 tumors. Grade 2 tumors were more cellular than grade 1 tumors and contained a greater degree of nuclear pleomorphism. Necrosis was occasionally present. Grade 3 chondrosarcomas showed even greater cellularity and pleomorphism than grade 2 tumors. Nuclear anaplasia was easily identified. Binucleate cells were frequent. Mitoses were variably observed. Necrosis was common and extensive.

In the assessment of grade, cellularity, mitosis, necrosis and cellular pleomorphism were evaluated subjectively; 1–3 points were given in an increasing order, from low to high grade. In the determination of the mitotic rate, the mitotic figures in at least 10 high power fields (HPF) were counted. Tumors with a mitotic count of 0 mitoses, 0–2 mitoses and those with more than 2 mitoses per 10 HPF were scored as 0, 1 and 2, respectively.

Pearson correlation coefficients were used to determine whether any correlation existed between Tl-201 uptake and tumor grade in chondrosarcoma.

### Statistical analyses

Statistical analyses were conducted using SPSS version 11.0 (SPSS Science, Chicago, IL, USA). Prior to statistical analyses, all the variables were examined through various SPSS programs for accuracy of data entry and missing values. Pearson correlation coefficients were used to

investigate if there was any correlation between Tl-201 uptake and tumor grade, cellularity, mitosis, necrosis and cellular pleomorphism in chondrosarcoma. All results were expressed as the mean + SD, and  $p$  values  $<0.05$  were considered to be statistically significant.

## Results

Patients' data and lesion characteristics are listed in Table 1. There were 7 enchondromas and 16 chondrosarcomas. There were no sex or age differences between the patients with enchondroma and chondrosarcoma. The mean size of the lesions in patients with enchondroma ( $5.0 \pm 3.2$  cm in maximum diameter) was smaller than that in those with chondrosarcoma ( $11.9 \pm 10.4$  cm in maximum diameter).

Tl-201 scintigraphy was true positive in 6 patients with chondrosarcoma and true negative in all patients with enchondroma. Tl-201 scintigraphy was false negative in 10 patients with chondrosarcoma. In these patients, no Tl-201 uptake was seen on early or late images. Four of 16 patients with chondrosarcoma were pathologically classified as grade 3, 5 as grade 2, and 7 had grade 1 chondrosarcoma.

One of 4 patients with grade 3 chondrosarcoma was diagnosed histopathologically as grade 3 chondrosarcoma with mesenchymal component (Fig. 1). Increased Tl-201 uptake was observed in all patients with grade 3 chondrosarcoma (Figs. 1, 2, 3) and 2 patients with grade 2 chondrosarcoma. No increased Tl-201 uptake was seen in patients with grade 1 chondrosarcoma (Fig. 4).

Early and delayed Tl-201 uptake scores and pathological details in patients with chondrosarcoma are given in Table 2. A significant correlation was found between Tl-201 uptake and tumor grade in chondrosarcoma ( $p = 0.002$ ,  $r = 0.71$ ). There was no correlation between Tl-201 uptake and the other pathological parameters.

## Discussion

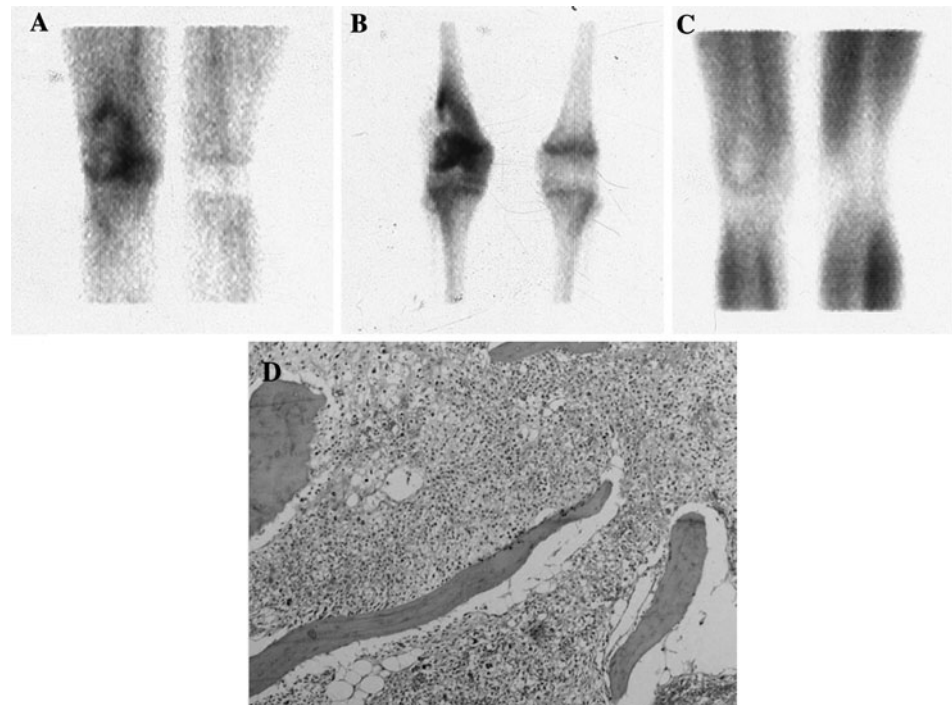
Tl-201 has been used as a tumor imaging agent for staging, radiotherapy planning and assessment of response to therapy, and evaluation of recurrence or residual tumor tissue in various tumors. The use of Tl-201 in differentiating malignant from benign lesions in bone and soft tissue sarcomas has also been reported [7–10]. When we reviewed the literature, mixed tumor groups such as

**Table 1** Patients' data and lesion characteristics

Patient number	Sex	Age	Localization	Maximum diameter (cm)	Pathological diagnosis
1	M	22	Femur–tibia	16	Chondrosarcoma
2	F	39	Scapula	5	Chondrosarcoma
3	F	30	Femur	10	Chondrosarcoma
4	M	38	Femur–tibia	12	Chondrosarcoma
5	M	55	Vertebra	8	Chondrosarcoma
6	M	49	Scapula	4	Chondrosarcoma
7	M	31	Humerus	12	Chondrosarcoma
8	M	63	Humerus	4	Chondrosarcoma
9	M	31	Metatarsal	2	Chondrosarcoma
10	M	33	Pelvis	7	Chondrosarcoma
11	F	51	Pelvis–femur	45	Chondrosarcoma
12	M	38	Pelvis	12	Chondrosarcoma
13	F	66	Humerus	6	Chondrosarcoma
14	F	54	Humerus	8	Chondrosarcoma
15	M	17	Femur	18	Chondrosarcoma with mesenchymal component
16	M	50	Thigh–pelvis	22	Chondrosarcoma
17	F	36	Humerus	3	Enchondroma
18	M	51	Humerus	8	Enchondroma
19	M	63	Femur	11	Enchondroma
20	F	72	Humerus	3	Enchondroma
21	M	34	Femur	4	Enchondroma
22	F	61	Femur	3	Enchondroma
23	M	37	Tibia	3	Enchondroma

Patients' numbers correspond to each other in Tables 1 and 2

**Fig. 1** A 17-year-old male patient was admitted to our hospital with a complaint of leg pain for 1 year. Three-phase bone scintigraphy and Tl-201 whole-body scintigraphy were performed preoperatively. Blood pool image (a) and late static image (b) of Tc-99m MDP 3-phase bone scintigraphy showed circumferential increased hyperemia and osteoblastic activity. Tl-201 scintigraphy showed mildly increased uptake compared with background activity in the lesion region (c). Pathology of resected specimen showed a grade 3 chondrosarcoma with mesenchymal component of the distal femur. The tumor showed the characteristic permeative pattern of medullary bone involvement (d) (patient number 15 in Tables 1, 2)



osteosarcoma, chondrosarcoma and synovial sarcoma were included in most of these studies. As far as we could determine, only a few studies have focused on the Tl-201 uptake pattern in specific subgroups of bone and soft tissue tumor groups. In our study, we investigated the results of Tl-201 tumor scintigraphy in cartilaginous tumors.

With regard to chondrosarcoma, especially low-grade chondrosarcoma, Tl-201 tumor imaging or Tc-99m tetrofosmin imaging results have been reported as false negative in 2 separate case reports [14, 15]. Lower tumor uptake ratios compared with osteosarcoma found in chondrosarcoma were obtained using different scintigraphic agents [16–21]. Similar to our results, Higuchi et al. [1] showed that enchondroma and most cases of grade 1 and grade 2 chondrosarcoma did not display increased Tl-201 uptake in the lesion. The difficulty in the differential diagnosis between grade 1 chondrosarcoma and enchondroma is a dilemma in terms of the diagnostic gold standard. In borderline cases between grade 1 chondrosarcoma and enchondroma, radiologic and scintigraphic findings might be helpful to the pathologist; diagnosis may be made more appropriately than relying on pure histopathological findings. However, we found no increased uptake in any of the patients with grade 1 chondrosarcoma or enchondroma. In 3 of 5 patients with grade 2 chondrosarcoma, Tl-201 scintigraphy did not help to distinguish between enchondroma and low-grade chondrosarcoma.

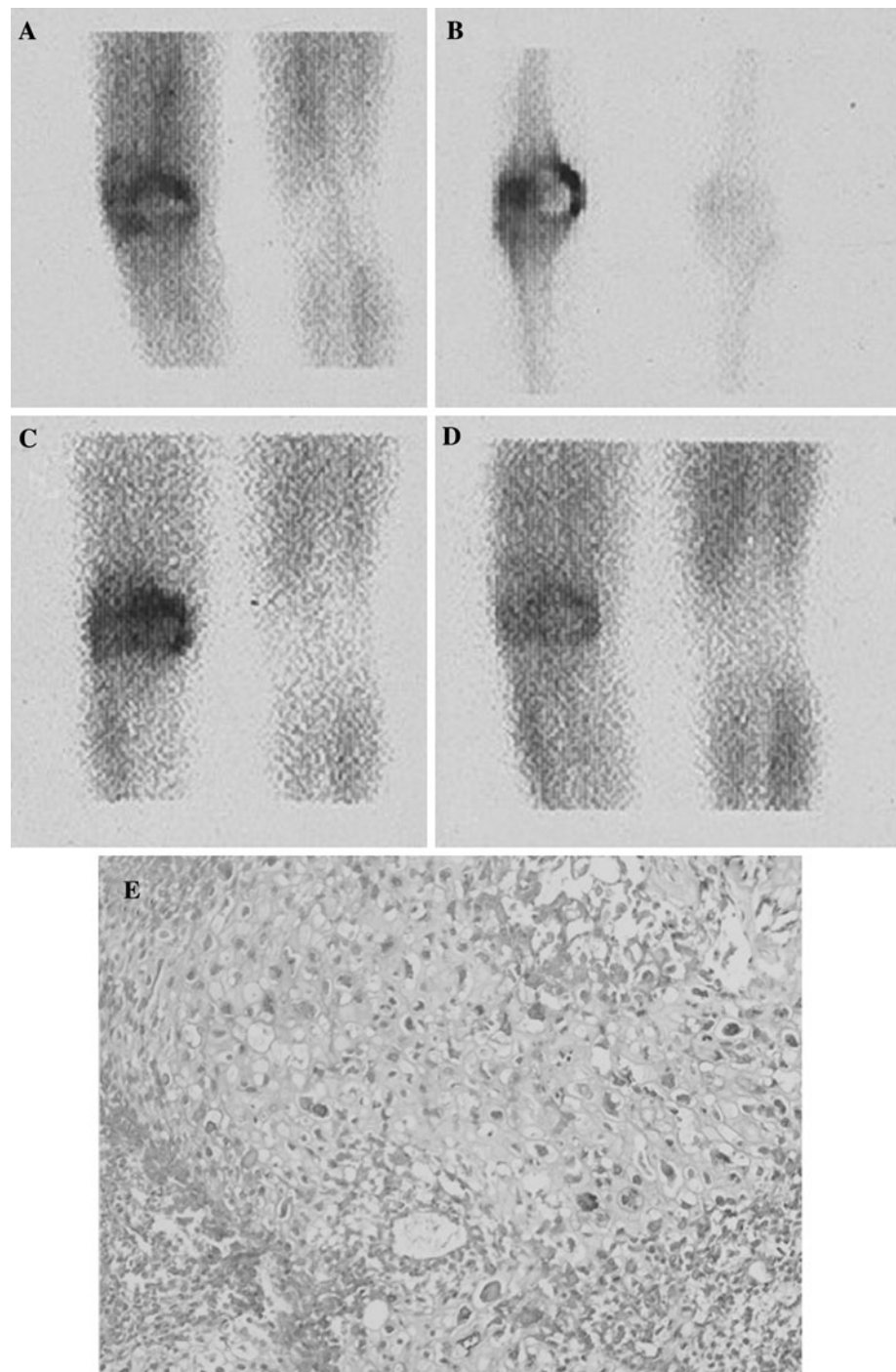
Three of 4 patients with grade 3 chondrosarcoma were diagnosed with conventional chondrosarcoma. Only 1

patient had grade 3 chondrosarcoma with mesenchymal component. We had only a limited number of patients with grade 3 chondrosarcoma. Three of 5 patients with grade 2 chondrosarcoma also had increased Tl-201 uptake in the tumor region. So, increased Tl-201 uptake in chondrosarcoma may be related to grade 2–3 chondrosarcoma in accordance with high malignant potential.

In one study investigating preoperative chemotherapy responses in patients with osteosarcoma, decreases in Tl-201 uptake correlated well with the degree of tumor necrosis [21–24]. Though it has been suggested that histological characteristics such as cell proliferative activities, dense cell compound and hypervascularity might have affected the uptake of Tl-201 in cartilaginous tumors in previous studies, the correlation between detailed pathologic parameters and Tl-201 uptake was first investigated in our study. While there was a correlation between the histopathologic grade of chondrosarcoma and Tl-201 uptake, no correlation was found in the other histopathologic parameters such as cellularity, nuclear pleomorphism, binucleated cells, mitotic figures, necrosis and tumor Tl-201 uptake. The correlations with binucleated cells, necrosis and Tl-201 uptake were not significant, but had a tendency to significance (for cell and necrosis  $r = 0.49$ ,  $p = 0.057$  and  $r = 0.49$ ,  $p = 0.054$ , respectively). The limited number of patients with high-grade chondrosarcoma in this study may have accounted for these results.

Almost all imaging studies including radiography, angiography, CT, MRI and nuclear medicine have been

**Fig. 2** A 38-year-old male patient had a complaint of right femur movement restriction for 6 months. Tc-99m MDP bone scintigraphy showed hyperemia and increased osteoblastic activity on blood pool image (a) and late static image (b). Early image of Tl-201 scintigraphy demonstrated increased uptake on distal femur–proximal tibia (c). Though partial washout was seen on late images, increased uptake compared with background activity was demonstrated on late images (d). The patient was operated on and diagnosed histopathologically with grade 3 chondrosarcoma of femur–tibia. The microscopic appearance of high-grade chondrosarcomas was characterized by increased cellularity and nuclear pleomorphism (e) (patient number 4 in Tables 1, 2)

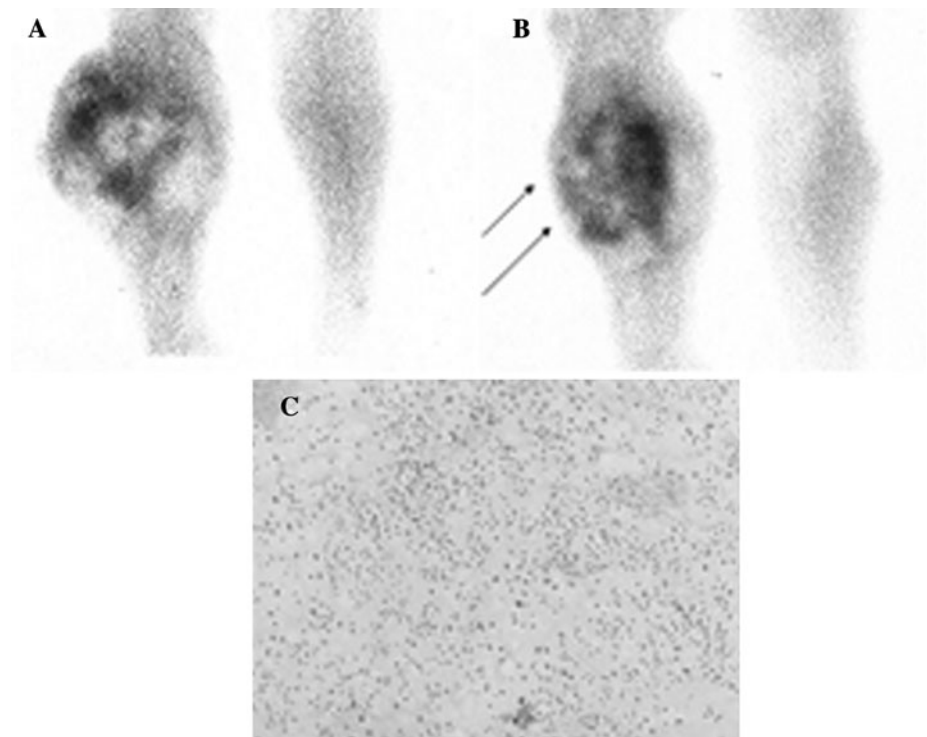


applied to the search for a means of resolving these problems [4, 6–15]. Anatomic details of the lesions are demonstrated well on computerized tomography and magnetic resonance images, but those modalities yield little information about the biologic activity of the tumors. Several authors have reported the usefulness of FDG-PET in these oncologic applications for musculoskeletal tumors

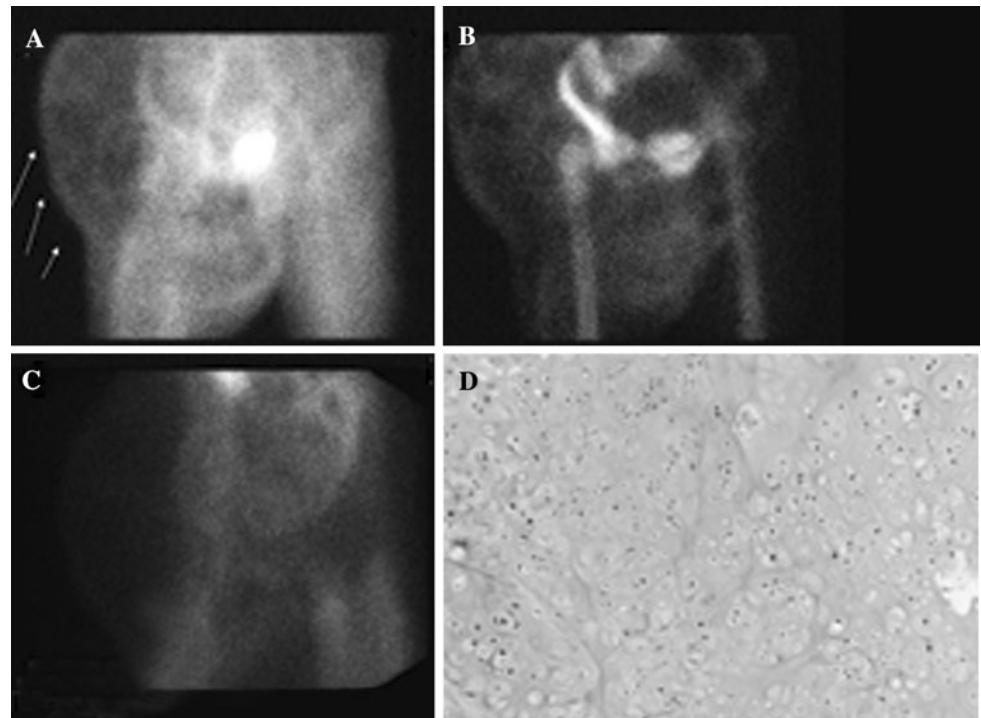
including various cell types [4, 5, 18, 21]. However, no sufficiently reliable method has been established. Though FDG-PET could be an objective and quantitative adjunct in the differential diagnosis and grading of chondrosarcoma, the results of published data have been controversial.

As a conclusion, we suggest 2 important results that were obtained in our study: first, Tl-201 uptake in

**Fig. 3** With a complaint of left leg pain and swelling on the upper part of the tibia, a 22-year-old male patient was admitted to our hospital. Three-phase bone scintigraphy showed increased activity on the distal femur–proximal tibia in accordance with a huge mass (not shown). Tl-201 scintigraphy showed heterogeneously increased Tl-201 uptake on both early (a) and delayed (b, arrows) Tl-201 images. Pathology of resected specimen demonstrated grade 3 chondrosarcoma of the femur–tibia. The tumor histopathologically showed increased cellularity and nuclear pleomorphism. An increased number of binucleate cells were seen (c) (patient number 1 in Tables 1, 2)



**Fig. 4** The patient, a 51-year-old woman, had symptoms of limitation of thigh movement, pain and palpable huge mass extending to the pelvis and thigh. Before that, she had not been admitted to hospital for this complaint. Tc-99m MDP 3-phase bone scintigraphy showed inhomogeneous mildly increased hyperemia on blood pool images (a, arrows) and osteoblastic activity on late static images (b) reflecting the tumor mass. No increased uptake on the tumor region compared with background activity was seen on Tl-201 scintigraphy (c). Grade 1 chondrosarcoma of the pelvis–femur was diagnosed histopathologically. The tumor was slightly hypercellular (d) (patient number 11 in Tables 1, 2)



chondrosarcoma was related to the pathological grade of tumor; second, this grade-related uptake of Tl-201 in chondrosarcoma could not differentiate enchondroma from

chondrosarcoma. Since both the studies demonstrating the uptake patterns in specific tumor groups would be valuable and F-18 FDG imaging results in chondrogenic tumors

**Table 2** Early and late Tl-201 uptake scores and pathological details in patients with chondrosarcoma

Patient number	Tl-201 uptake score		Histopathological findings					
	Early	Delayed	Grade	Cellularity	Mitotic activity	Necrosis	Binucleated cells	Nuclear pleomorphism
1	2	2	3	3	2	2	2	3
2	1	1	2	2	1	1	2	2
3	2	2	2	2	1	2	2	2
4	2	2	3	3	2	2	2	3
5	1	1	1	1	1	0	1	1
6	1	1	2	2	1	1	2	2
7	2	2	2	2	1	1	2	2
8	1	1	1	2	0	0	2	2
9	2	2	3	2	0	0	2	2
10	1	1	1	2	0	0	1	1
11	1	1	1	2	1	1	2	2
12	1	1	1	1	0	1	1	2
13	1	1	1	2	1	1	2	2
14	1	1	1	3	3	2	2	3
15	2	2	3	3	1	2	2	2
16	1	1	2	2	0	0	2	2

Patients' numbers correspond to each other in Tables 1 and 2

described in literature have been controversial, performing dual point F-18 FDG imaging in cartilaginous tumors from the viewpoint of diagnosis would be the next step of our study.

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