Title “Diagnostic value of Thallium-201 scintigraphy in differentiating malignant bone tumors from benign bone lesions.“

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None

Abstract

Objective This retrospective study aims to evaluate the diagnostic capacity of thallium-201 (201-Tl) scintigraphy for differentiating malignant bone tumors from benign bone lesions.

Methods Between January 2006 and December 2012, 279 patients with bone lesions (51 malignant and 228 benign) underwent 201-Tl scintigraphy before treatment. To evaluate 201-Tl uptake, we investigated tumor-to-background contrast (TBC) as well as TBC washout rate (WR). The differences of TBC on early and delayed images and WR were estimated by the Mann-Whitney U test. Receiver operating characteristic (ROC) analyses were used to determine the cut-off TBC values for differentiating malignant bone tumors from benign bone lesions.

Results There were statistically significant differences in median TBC between malignant tumors and benign lesions. These differences occurred for early imaging (1.57 vs. 0.09, $p < 0.001$) as well as for delayed imaging (0.83 vs. 0.07, $p<0.001$). However, there was no statistical difference in WR between malignant tumors and benign lesions (44% vs. 43%, NS). The chosen TBC cut-off value was 0.68 for early imaging and 0.38 for delayed imaging. Using these cut-off values, the prediction of

malignancy had a 77% sensitivity, 74% specificity, and 75% accuracy for early imaging and an 80% sensitivity, 76% specificity, and 77% accuracy for delayed imaging.

Conclusions 201-Tl scintigraphy may have the ability to distinguish malignant bone tumors from benign bone lesions.

Key word

Thallium-201 scintigraphy・Malignant bone tumor・Benign bone tumor・Receiver operating characteristic (ROC) analysis・Tumor-to-background contrast (TBC)

Introduction

Bone tumors consist of a large number of histological types and origins. Bone tumors are categorized as 1) benign, 2) locally aggressive or rarely metastasizing, 3) malignant on the basis of the Third Edition of the WHO Classification of tumors of soft tissue and bone [1]. Morphologic tumor images are provided by radiography, computed tomography (CT), and magnetic resonance imaging (MRI). These modalities are the clinical diagnostic imaging tools for detecting bone tumors. The recognition and diagnosis of malignancy is not very difficult with the typical findings from history, physical examination, and radiological imaging. On the other hand, it is not easy to diagnose a bone tumor with atypical findings.

Nuclear medicine images offer specific biological and metabolic information but still using a non-invasive approach. Thallium-201 (201-Tl) scintigraphy has traditionally been used for measurement of myocardial perfusion. However, in clinical oncology, this radionuclide has an affinity for a variety of neoplasms and 201-Tl scintigraphy has been used since the 1980s as a functional imaging tool for various tumors [2]. There has been growing interest in using 201-Tl scintigraphy for management of bone and soft tissue tumors since the early 1990s [3]. Several studies

have reported 201-Tl scintigraphy to be an effective diagnostic tool to differentiate malignant from benign areas of interest [2-11]. However, there is little published data for 201-Tl scintigraphy dealing with only bone lesions [3] and no report has statistically evaluated the diagnostic capacity of 201-Tl scintigraphy in a large number of bone lesions. Therefore, we speculated that 201-Tl scintigraphy has the potential to be a useful tool to differentiate malignant from benign bone lesions and to be the same for soft tissue areas of interest [9].

In the present study, we retrospectively reviewed 279 consecutive cases and evaluated whether 201-Tl scintigraphy was an indicator of malignancy in bone lesions. We employed a semi-quantitative analyses based on tumor-to-background contrast (TBC) measured for not only 15-min early imaging but also 2-h delayed-imaging, and also on washout rate (WR).

Materials and Methods

Study Population

This retrospective study included 279 consecutive patients with a primary bone lesion (126 female, 153 male; mean age, 34 years; range, 4–85 years), who underwent 201-Tl scintigraphy without previous chemotherapy and radiotherapy between January 2006 and December 2012. We excluded the patients with bone metastases from another organ to focus on the evaluation of primary bone lesions. All patients underwent histological examinations or were followed up with imaging investigations for more than 12 months. Histological examination identified 51 lesions as malignant and 126 as benign. Another 102 benign lesions were diagnosed as benign by virtue of no change in size on CT or MRI during a 12-month follow-up. This retrospective study was approved by the hospital ethics committee, which waived informed consent from the patients.

201-Tl Scintigraphy

The scintigraphy with 201-Tl was performed per institutional protocol: that is, an intravenous bolus of 74 MBq (2mCi) of 201-Tl was administered, and scintigraphic planar images were obtained using a conventional gamma camera system (GCA-7200A/DI, Toshiba, Tokyo, Japan) at 15 minutes (early imaging) and 2 hours (delayed imaging) after the injection. A low energy, high resolution, parallel-hole

collimator was used and images were acquired into a 512×512 matrix for 10 minutes. We used anterior and posterior planar images for the semi-quantitative evaluation.

Image Data Analysis

Two physicians who were unaware of the histological and imaging-follow-up results made the measurements and interpreted all findings by consensus on radiography and 201-Tl scintigraphy.

On radiography, we set the criteria of finding to distinguish benign and malignant bone tumors. Those findings were the ill defined margin, the moth-eaten or permeative bone destruction, the destruction of cortical bone, and the periosteal response like sunburst appearance. When any of the above findings showed, we considered it as a malignant tumor by two physicians' agreement.

On 201-Tl scintigraphy, two equally-sized regions of interest (ROI) were compared for each image (Fig. 1a-c). The first ROI was focused on the lesion itself (that is, on the suspected tumor). To serve as the background, a second ROI was placed on the contralateral side or on an area adjacent to the lesion in where the tissue was normal

[12]. When 201-Tl uptake was not detectable on the image, the ROI was placed on the area corresponding to the suspect area as identified by radiography, CT or MRI (Fig. 2a-c). We calculated tumor-to-background contrast (TBC) using the average counts per pixel in the ROI for the tumor area (T) and that value for the background area (BG). That is, TBC = (T - BG)/BG. Moreover, we calculated WR from the TBC value at the early Imaging time (TE) and that at the delayed imaging time (TD) as follows: WR = {(TE - TD)/ TE} × 100.

Statistical Analysis

Differences in the TBC between early and delayed imaging and WR were analyzed with the Mann-Whitney's U test. Receiver operating characteristic (ROC) analyses were used to determine the TBC value that would maximize the sensitivity and specificity of tumor detection. ROC curves plotted true-positive rate (sensitivity) versus false positive rate (1-specificity). All analyses were performed with the IBM SPSS Statistics 22 for Windows software package (IBM Corp., Armonk, NY, USA). Probability values < 0.05 were considered statistically significant.

Results

There were 51 malignant bone tumors and 228 benign bone lesions (Table 1, 2). Of all bone lesions, 181 were located in the lower extremity, 58 in the upper extremity, and 40 in the trunk. TBC was obtained for all malignant tumors and benign lesions for both early and delayed imaging.

Median TBC of all benign lesions was 0.09 (interquartile range, 0.03 to 0.71) on early imaging and 0.07 (interquartile range, 0.02 to 0.36) on delayed imaging. Median TBC of all malignant tumors was 1.57 (interquartile range, 0.68 to 3.12) on early imaging and 0.83 (interquartile range, 0.39 to 1.65) on delayed imaging. Median TBC of malignant tumors was significantly higher than that of benign lesions at both early and delayed imaging times (each $p < 0.0001$) (Fig. 3a-b). In contrast, WR averaged 43% (interquartile range, -18 to 58) for all benign lesions and 44% (interquartile range, 32 to 52) for all malignant tumors, so that there was no statistical difference (Fig. 3c). Furthermore, the cut-off value for TBC with early imaging was 0.68 for the highest accuracy (75%) for detecting malignant bone tumors, yielding a sensitivity of 77% and a specificity of 74%. For delayed imaging, the cut-off value was 0.38, yielding a sensitivity of 80%, a specificity of 76%, and an accuracy of 77%. The

area under the ROC curve (AUC) was almost the same for early and delayed imaging (0.810±0.029 vs. 0.805±0.031) (Fig. 4).

On the other hands, the sensitivity, specificity and accuracy of the performance on radiography were 48%, 92%, and 84% in differentiating malignant bone tumors from benign bone lesions. False-positive results on radiography were found in 18 benign lesions, which were reduced to 9 false positive cases by the cut-off values of 201-Tl scintigraphy on early and delayed imaging. False-negative results on radiography were found in 27 malignant tumors, which were reduced to 21 cases on early imaging and to 22 cases on delayed imaging in 201-Tl scintigraphy.

On early imaging, false-negative results (TBC of less than 0.68) were found in 12 malignant tumors (9 chondrosarcomas, 1 chordoma, 1 Ewing sarcoma, 1 osteosarcoma). On delayed imaging, false-negative results (TBC of less than 0.38) were found in 10 malignant tumors（1 chondrosarcoma and 1 chordoma became true-positive）. On early imaging, false-positive results (TBC of > 0.68) were found for 58 benign lesions (20 giant cell tumors, 7 osteofibrous dysplasias, 6 non-ossifying fibromas, 6 chondroblastomas, 2 aneurysmal bone cysts, 2 fibrous dysplasias, 2 simple bone cysts, 2 histiocytosis, 2 enchondromas, 2 osteoid osteomas, 2 others, 2

inflammatory lesions, 1 granulation, 1 Paget disease, 1 melorheostosis). On delayed imaging, false-positive results (TBC of > 0.38) were found in 54 benign lesions (2 non-ossifying fibromas, 1 cortical defect, and 1 osteofibrous dysplasia became true-negative results).

Discussion

The present study assessed the usefulness of 201-Tl scintigraphy and semi-quantitative analysis for patients suspected of having malignant bone tumors. The median TBC of malignant tumors was significantly higher than that for benign lesions on both early and delayed images. The cut-off values of TBC were set with acceptable accuracy for both.

The diagnosis of malignant bone tumors is not always easy with conventional radiologic modalities including radiography, CT, and MRI, those which provide excellent morphologic delineation and localization of bone tumors. Functional nuclear scans reflect the metabolic activity of tumors and may provide important information regarding the biologic behavior. 201-Tl scintigraphy has been used in clinical oncology to estimate the presence and biologic activity of tumors including bone and soft tissue

tumors and the utility of 201-Tl scintigraphy has been reported to differentiate malignant tumors from benign lesions in bone and soft tissue [2-14]. However, these previous studies were composed of a relatively small number of bone tumors and most of the studies used only visual analysis [2, 3, 5]. In the present study, we evaluated the diagnostic capacity of 201-Tl scintigraphy for a large number of bone lesions and employed semi-quantitative analysis.

The first major finding of our study was that median TBC of 201-Tl scintigraphy was significantly higher in malignant bone tumors than it was in benign bone lesions at both the 15-min early time point and the 2-h delayed time point. On the other hand, there was no statistical difference in WR between malignant tumors and benign bone lesions. The previous study analyzed the diagnostic capacity of 201-Tl scintigraphy using semi-quantitative analysis for 12 malignant bone tumors and 14 benign bone lesions [3]. It demonstrated that the count ratio of lesion-to-normal tissue (L/N ratio), which approximately corresponds to TBC in the present study, was significantly higher in malignant tumors than in benign lesions and decreased on delayed imaging mainly due to the increase in surrounding normal muscle uptake.

Previous articles suggested the usefulness of WR on 201-Tl scintigraphy in various organs. However, in bone and soft tissue tumors, some investigators have showed no statistical significance of WR in the semi-quantitative analysis of 201-Tl scintigraphy [3, 5, 8]. Sugawara et al. [8] described WR was substantially affected by the change of normal muscle uptake rather than the change of tumor uptake. In the present study, no significant difference was found in WR between benign and malignant bone lesions. We considered that no statistical significance of WR might be due to relatively small volume of bone lesion compared with surrounding soft tissue and the change of 201-Tl uptake to the surrounding muscle had the bigger impact on WR in both benign and malignant bone lesions. According to the previous reports [2,4,7,12,15-22], 201-Tl uptake depends on cell viability and metabolic condition and a high metabolic rate with malignancy was the most important factor determining differences in 201-Tl uptake between malignant tumors and benign lesions. Moreover, 201-Tl uptake on early imaging is affected by tumor vascularity and cellularity. Those findings suggested that 201-Tl uptake would predict the biologic aggressiveness in bone lesions and the semi-quantitative analysis of 201-Tl uptake would be useful tool for differentiating the state of malignancy from benignity in bone lesions on both early and delayed images,

and suggested that WR would not be predictor of malignancy in bone lesions.

The second important finding of our study was that the cut-off value of TBC can be set with acceptable diagnostic accuracy, that is with an accuracy of 75% for early imaging and of 77% for delayed imaging, and that the AUC is nearly the same for both. There had been no study evaluating the diagnostic capacity of 201-Tl scintigraphy with the cut-off values and the AUC determined for both early and delayed imaging of bone lesions. Our results showed the diagnostic accuracy and the AUC were similar for early and delayed imaging. However, the number of false-negatives and the number of false-positives were both smaller for 2-h delayed imaging compared to 15-min early imaging. These findings indicate that 2-h delayed 201-Tl imaging may have the potential to decrease the false-negative and false-positive cases while being equal in accuracy to 15-min early 201-Tl imaging for the diagnosis of bone tumors. Therefore, we thought that delayed imaging is also necessary to keep the diagnostic accuracy, as well as early imaging. Besides, these cut-off values in 201-Tl scintigraphy reduced false-positive and false-negative results on radiography. Especially, a half of false-positive cases was improved to be true-negative. In our study, the sensitivity on radiography showed to be low. We speculated this low sensitivity was due to the

difficulty for identification of the bone lesion in the trunk (i.e., vertebrae, rib) on radiography. Our study showed 201-Tl scintigraphy further improved the diagnostic power of radiography, especially in the sensitivity.

The third important finding of our study was a predictable trend in false-positive and false-negative results. In false-positive results, all giant cell tumors (GCT), which is considered benign tumor, showed higher 201-Tl uptake than the cut-off values on both early and delayed imagings. GCT has been reported to be characteristic by hypercellularity and hypervascularity and these histologic features may contribute to the consistent 201-Tl uptake in GCT [2]. On the other hand, most of all chondrosarcoma showed lower uptake than the cut-off values. In the previous report, this behavior has been seemed to be the result of the poor vascularity and less cellular matrix [7]. Thus the characteristics of tumor component, such as the cellularity, vascularity, and intercellular matrix, result in false positive by GCT and false negative by chondrosarcoma.

Positron emission tomography (PET) with 2-［F-18］fluoro-2-deoxy-D-glucose (FDG) is a well-established functional diagnostic oncologic imaging technique that provides information about glucose metabolism in the

assessment of lesions. Maximum standardized uptake value (SUV max) has been measured to evaluate FDG uptake. There are several reports about the usefulness of F-18 FDG-PET in bone and soft tissue tumors [23-29]. However, a considerable overlap in SUV max was observed between benign lesions and malignant tumors. Therefore, the ability of F-18 FDG-PET to distinguish between benign and malignant in evaluating the possibility of bone and soft tissue tumors has been designated as controversial [25-27]. On the other hand, one previous study reported the sensitivity, specificity, and accuracy of F-18 FDG-PET calculated by ROC curve analyses, which included 47 (27 benign, 20 malignant) bone lesions [29]. The study showed the cut-off value of SUV max was 3.7 for the highest accuracy for detecting malignant bone tumors, yielding a sensitivity of 80%, a specificity of 63%, and an accuracy of 70%. Compared with the 201-Tl scintigraphy in the present study, the sensitivity of F-18 FDG-PET was at the same level. The specificity and accuracy of F-18 FDG-PET was lower than that of delayed imaging with 201-Tl scintigraphy. However, we could not determine which modality is more useful imaging tool as yet. Further prospective investigation in a large number of patients is necessary to compare with the diagnostic capacity of 201-Tl scintigraphy and FDG PET/CT.

Our study has several limitations. First, it was a retrospective study. Second, we calculated TBC on only planar images. For sites including considerable muscle tissue (i.e., trunk, thigh), uptake in overlying physiological muscle made it difficult to evaluate tumor uptake precisely. Further prospective investigations with both planar imaging and single-photon-emission computed tomography would be useful to evaluate the diagnostic capacity of 201-Tl scintigraphy to differentiate between malignant tumors and benign bone lesions. Finally, there were not a few false-negative and false-positive results using only the semi-quantitative analysis. Thus it might be advantageous to carry out an evaluation with multi-modality imaging, using CT, or MRI. On the other hand, this semi-quantitative analysis is composed of a simple measuring procedure on planar images; such an analysis is very amenable to clinical practice. It can potentially increase the diagnostic capacity for bone tumors compared to visual analysis.

In conclusion, median TBC on both early and delayed 201-Tl scintigraphy was found to be significantly higher in malignant bone tumors than benign bone lesions. A TBC of at least 0.68 on 15-min early imaging and of at least 0.38 on 2-h delayed imaging were important indicators of malignancy that lead to an acceptable level of

accuracy for detecting malignant bone tumors. In summary, 201-Tl scintigraphy may be an effective diagnostic modality to differentiate malignant bone tumors from benign bone lesions.

References

1. Fletcher CDM, Unni KK, Mertens F. WHO Classification of Tumours. Pathology and Genetics of Tumours of Soft tissue and Bone. 3rd ed. Lyon: International Agency for Research on Cancer; 2002.

2. Sato O, Kawai A, Ozaki T, Kunisada T, Danura T, Inoue H. Value of thallium-201 scintigraphy in bone and soft tissue tumors. Journal of orthopaedic science: official journal of the Japanese Orthopaedic Association. 1998;3:297-303.

3. Goto Y, Ihara K, Kawauchi S, Ohi R, Sasaki K, Kawai S. Clinical significance of thallium-201 scintigraphy in bone and soft tissue tumors. Journal of orthopaedic science: official journal of the Japanese Orthopaedic Association. 2002;7:304-12.

4. Caluser CI, Abdel-Dayem HM, Macapinlac HA, Scott A, Healey JH, Huvos A, et al. The value of thallium and three-phase bone scans in the evaluation of bone and soft tissue sarcomas. European journal of nuclear medicine. 1994;21:1198-205.

5. Matsui R, Komori T, Nakata Y, Doi K, Tabuchi K, Saika Y, et al. [Quantitative assessment of 201Tl-SPECT in tumors of bone and soft tissue]. Kaku igaku The Japanese journal of nuclear medicine. 1999;36:219-28.

6. Nishiyama Y, Yamamoto Y, Toyama Y, Satoh K, Ohkawa M, Tanabe M. Diagnostic value of TI-201 and three-phase bone scintigraphy for bone and soft-tissue tumors. Clinical nuclear medicine. 2000;25:200-5.

7. Sumiya H, Taki J, Higuchi T, Tonami N. Nuclear imaging of bone tumors: thallium-201 scintigraphy. Seminars in musculoskeletal radiology. 2001;5:177-82.

8. Sugawara Y, Kikuchi T, Kajihara M, Semba T, Ochi T, Fujii T, et al. Thallium-201 scintigraphy in bone and soft-tissue tumors: a comparison of dynamic, early and delayed scans. Annals of nuclear medicine. 2005;19:461-8.

9. Kawakami N, Kunisada T, Sato S, Morimoto Y, Tanaka M, Sasaki T, et al. Thallium-201 scintigraphy is an effective diagnostic modality to distinguish malignant from benign soft-tissue tumors. Clinical nuclear medicine. 2011;36:982-6.

10. Yamamoto Y, Kawaguchi Y, Kawase Y, Maeda Y, Nishiyama Y. A comparative study of F-18 FDG PET and 201Tl scintigraphy for detection of primary malignant bone and soft-tissue tumors. Clinical nuclear medicine. 2011;36:290-4.

11. Yamamoto Y, Kawaguchi Y, Kawase Y, Maeda Y, Nishiyama Y. A comparative study of F-18 FDG PET and 201Tl scintigraphy for detection of primary malignant bone and soft-tissue tumors. Clinical nuclear medicine. 2011;36:290-4.

12. Kunisada T, Ozaki T, Kawai A, Sugihara S, Taguchi K, Inoue H. Imaging assessment of the responses of osteosarcoma patients to preoperative chemotherapy: angiography compared with thallium-201 scintigraphy. Cancer. 1999;86:949-56.

13. Abdel-Dayem HM. The role of nuclear medicine in primary bone and soft tissue tumors. Seminars in nuclear medicine. 1997;27:355-63.

14. Elgazzar AH, Malki AA, Abdel-Dayem HM, Mahmoud A, Sahweil A, Razzak S, et al. Role of thallium-201 in the diagnosis of solitary bone lesions. Nuclear medicine communications. 1989;10:477-85.

15. Menendez LR, Fideler BM, Mirra J. Thallium-201 scanning for the evaluation of osteosarcoma and soft-tissue sarcoma. A study of the evaluation and predictability of the histological response to chemotherapy. The Journal of bone and joint surgery American volume. 1993;75:526-31.

16. Terui S, Terauchi T, Abe H, Fukuma H, Beppu Y, Chuman K, et al. On clinical usefulness of Tl-201 scintigraphy for the management of malignant soft tissue tumors. Annals of nuclear medicine. 1994;8:55-64.

17. Lin J, Leung WT, Ho SK, Ho KC, Kumta SM, Metreweli C, et al. Quantitative evaluation of thallium-201 uptake in predicting chemotherapeutic response of osteosarcoma. European journal of nuclear medicine. 1995;22:553-5.

18. Adalet I, Ozger H, Cantez S. Comparison of Tc-99m MIBI and Tl-201 uptake in musculoskeletal lesions. Clinical nuclear medicine. 1996;21:118-21.

19. Abe H, Terui S, Terauchi T, Muramatsu Y, Yokayama R, Ohtomo K, et al. Comparison of Tc-99m pertechnetate with Tl-201 and Ga-67 scintigraphy of malignant soft-tissue tumors. Clinical nuclear medicine. 1997;22:38-41.

20. Imbriaco M, Yeh SD, Yeung H, Zhang JJ, Healey JH, Meyers P, et al. Thallium-201 scintigraphy for the evaluation of tumor response to preoperative chemotherapy in patients with osteosarcoma. Cancer. 1997;80:1507-12.

21. Taki J, Sumiya H, Tsuchiya H, Tomita K, Nonomura A, Tonami N. Evaluating benign and malignant bone and soft-tissue lesions with technetium-99m-MIBI scintigraphy. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 1997;38:501-6.

22. Sumiya H, Taki J, Tsuchiya H, Nonomura A, Miyauchi T, Tonami N. Midcourse thallium-201 scintigraphy to predict tumor response in bone and soft-tissue tumors. Journal of nuclear medicine: official publication, Society of Nuclear Medicine. 19;39(9):1600-4.

23. Adler LP, Blair HF, Makley JT, Williams RP, Joyce MJ, Leisure G, et al. Noninvasive grading of musculoskeletal tumors using PET. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 1991;32:1508-12.

24. Dehdashti F, Siegel BA, Griffeth LK, Fusselman MJ, Trask DD, McGuire AH, et al. Benign versus malignant intraosseous lesions: discrimination by means of PET with 2-[F-18] fluoro-2-deoxy-D-glucose. Radiology. 1996;200:243-7.

25. Schulte M, Brecht-Krauss D, Heymer B, Guhlmann A, Hartwig E, Sarkar MR, et al. Grading of tumors and tumorlike lesions of bone: evaluation by FDG PET. Journal of nuclear medicine: official publication, Society of Nuclear Medicine. 2000;41:1695-701.

26. Aoki J, Watanabe H, Shinozaki T, Takagishi K, Ishijima H, Oya N, et al. FDG PET of primary benign and malignant bone tumors: standardized uptake value in 52 lesions. Radiology. 2001;219:774-7.

27. Aoki J, Watanabe H, Shinozaki T, Takagishi K, Tokunaga M, Koyama Y, et al. FDG-PET for preoperative differential diagnosis between benign and malignant soft tissue masses. Skeletal radiology. 2003;32:133-8.

28. Bastiaannet E, Groen H, Jager PL, Cobben DC, van der Graaf WT, Vaalburg W, et al. The value of FDG-PET in the detection, grading and response to therapy of soft tissue and bone

sarcomas; a systematic review and meta-analysis. Cancer treatment reviews. 2004;30:83-101.

29. Shin DS, Shon OJ, Han DS, Choi JH, Chun KA, Cho IH. The clinical efficacy of (18) F-FDG-PET/CT in benign and malignant musculoskeletal tumors. Annals of nuclear medicine. 2008;22:603-9.

Figure Legends

Fig. 1a-c Osteosarcoma in the left distal femur. Coronal T2WI MR images with fat saturation (**a**). Early imaging of 201-Tl scintigraphy (**b**). Delayed imaging of 201-Tl scintigraphy (**c**). The first ROI (*) was placed on the outer border of the lesion and the second ROI (**) was placed on the contralateral side, which served as the background. TBC on early and delayed imaging are 1.54 and 0.83, respectively.

Fig. 2a-c Simple bone cyst in the right proximal femur. Radiography reveals the lesion (*arrow*, **a**). Early imaging of 201-Tl scintigraphy (**b**). Delayed imaging of 201-Tl scintigraphy (**c**). Both images show no significant uptake of 201-Tl. We obtained the area corresponding to the lesion(*) and the background(**) by radiography. TBC on early and delayed image is 0.01 and 0.02, respectively.

Fig. 3a-c Uptake of 201-Tl between benign and malignant bone tumor. **a** TBC on early imaging, **b** TBC on delayed imaging, **c** WR calculated from the two imaging time points.

Fig. 4 ROC analysis of TBC of 201-Tl on early and delayed imaging. It shows the two graphed lines, that is, eTBC is the plot corresponding to TBC values from early imaging and dTBC is the plot corresponding to TBC values from delayed imaging.

Table

Table 1 Mean TBC and WR of 228 patients with benign bone lesions.

		Mean TBC		WR
	n	early	delayed	(%)
Giant cell tumor	20	4.64 ± 3.37	2.40 ± 1.41	43 ± 14
Aneurysmal bone cyst	6	1.96 ± 2.93	1.13 ± 1.62	-117 ± 317
Histiocytosis	3	1.69 ± 1.63	0.84 ± 0.83	51 ± 1
Chondroblastoma	9	1.54 ± 0.90	0.80 ± 0.57	53 ± 19
Osteoid osteoma	5	0.97 ± 1.04	0.55 ± 0.57	28 ± 49
Melorheostosis	2	0.86 ± 0.83	0.49 ± 0.48	52 ± 10
Non ossifying fibroma	15	0.87 ± 1.32	0.47 ± 0.74	-253 ± 776
Osteofibrous dysplasia	11	0.88 ± 0.77	0.46 ± 0.36	-266 ± 927
Inflammatory lesion	5	1.08 ± 1.29	0.44 ± 0.54	-149 ± 420
Paget disease	2	0.89 ± 0.89	0.29 ± 0.28	-345 ± 413
Granulation	4	0.26 ± 0.32	0.24 ± 0.17	-92 ± 101
Other	11	0.51 ± 0.92	0.17 ± 0.22	-38 ± 260
Osteonecrosis	4	0.27 ± 0.23	0.17 ± 0.14	36 ± 11
Lipoma	2	0.08 ± 0.02	0.13 ± 0.06	-46 ± 40
Hemangioma	4	0.09 ± 0.03	0.12 ± 0.07	-17 ± 64
Enchondroma	29	0.18 ± 0.33	0.11 ± 0.19	-20 ± 121
Fibrous dysplasia	40	0.18 ± 0.25	0.10 ± 0.15	4 ± 119
Cortical defect	6	0.18 ± 0.24	0.09 ± 0.08	7 ± 59
Simple bone cyst	19	0.14 ± 0.22	0.09 ± 0.19	24 ± 55
Osteochondroma	20	0.09 ± 0.10	0.06 ± 0.06	-122 ± 23
Ganglion cyst	9	0.07 ± 0.06	0.05 ± 0.03	-14 ± 79
Benign fibrous histiocytoma	2	0.01 ± 0.01	0.01 ± 0.01	-93 ± 172

TBC tumor-to-background contrast, *WR* washout rate

Table 2 Mean TBC and WR of 51 patients with malignant bone tumors.

		Mean TBC		WR
	n	Early	delayed	(%)
Plasmacytoma	1	11.91	6.02	49
Malignant Giant cell tumor	1	10.04	5.93	41
Malignant fibrous histiocytoma	2	4.99 ± 2.61	2.72 ± 2.01	23 ± 4
Osteosarcoma	29	2.54 ± 1.78	1.29 ± 1.06	46 ± 15
Malignant lymphoma	4	1.82 ± 0.65	1.14 ± 0.35	35 ± 10
Ewing sarcoma	3	1.47 ± 1.35	0.87 ± 0.81	42 ± 1
Chordoma	1	0.58	0.75	-30
Chondrosarcoma	10	0.28 ± 0.22	0.17 ± 0.16	42 ± 24

TBC tumor-to-background contrast, *WR* washout rate

Fig. 1

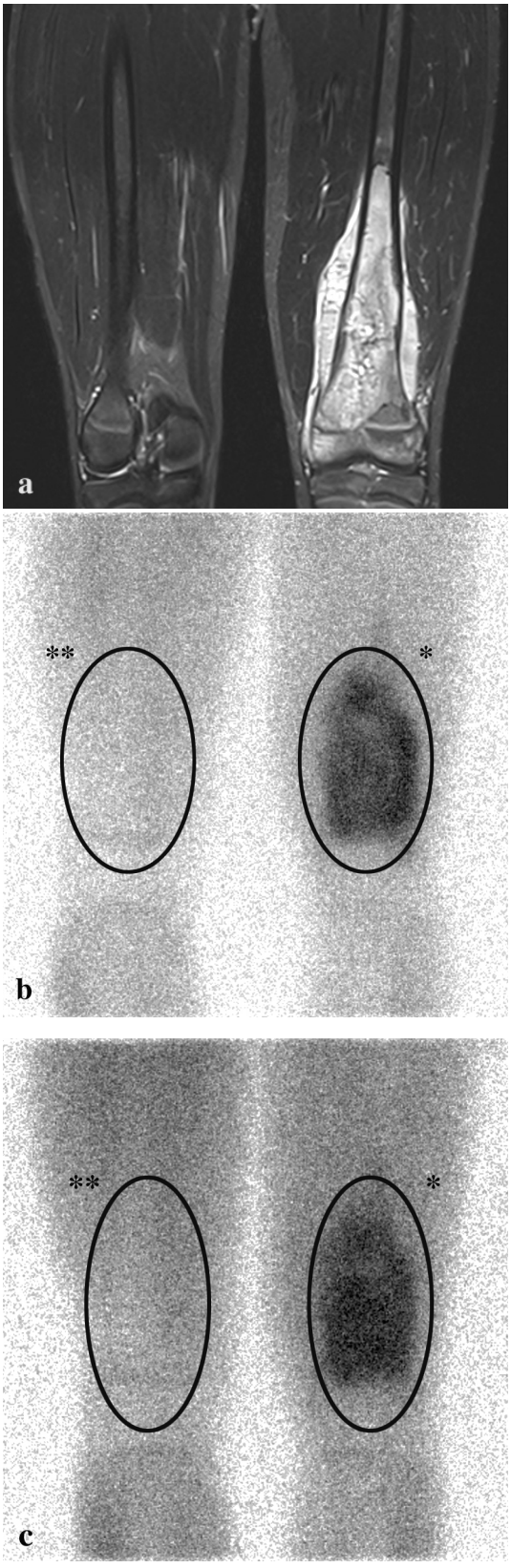


Fig. 2

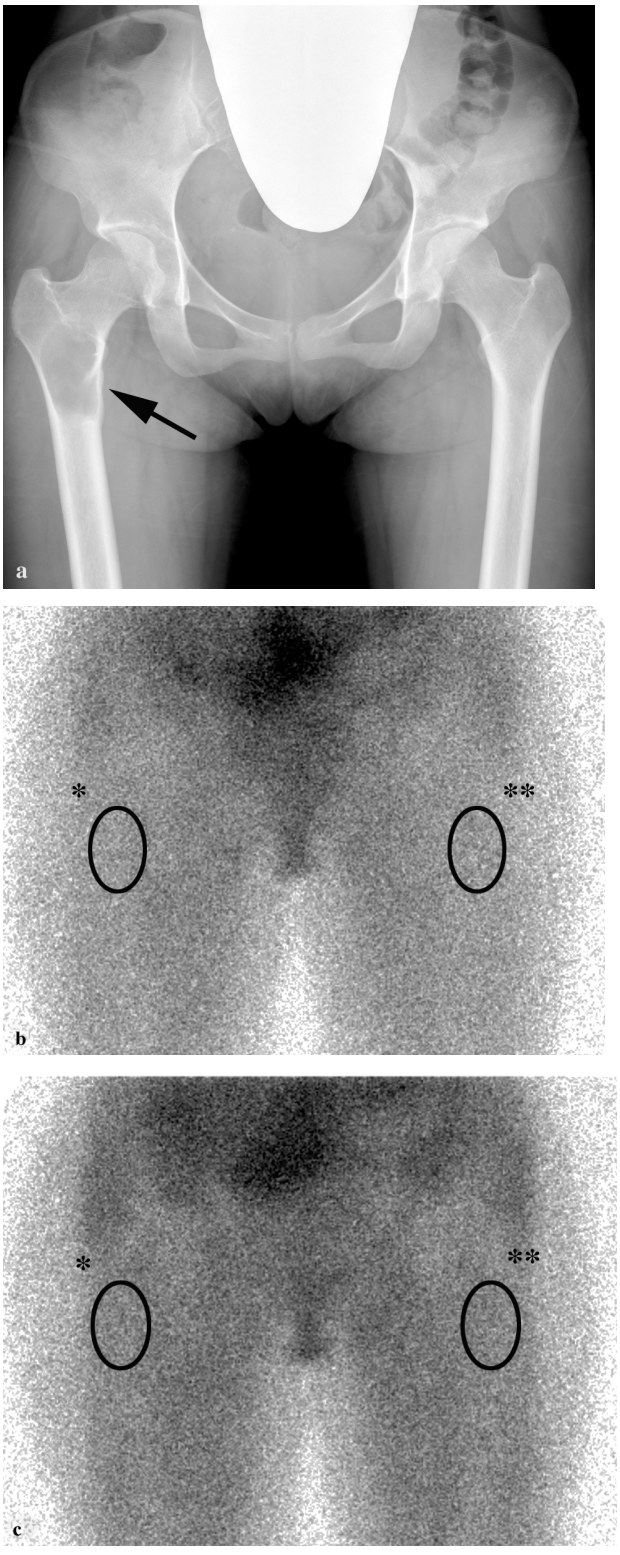
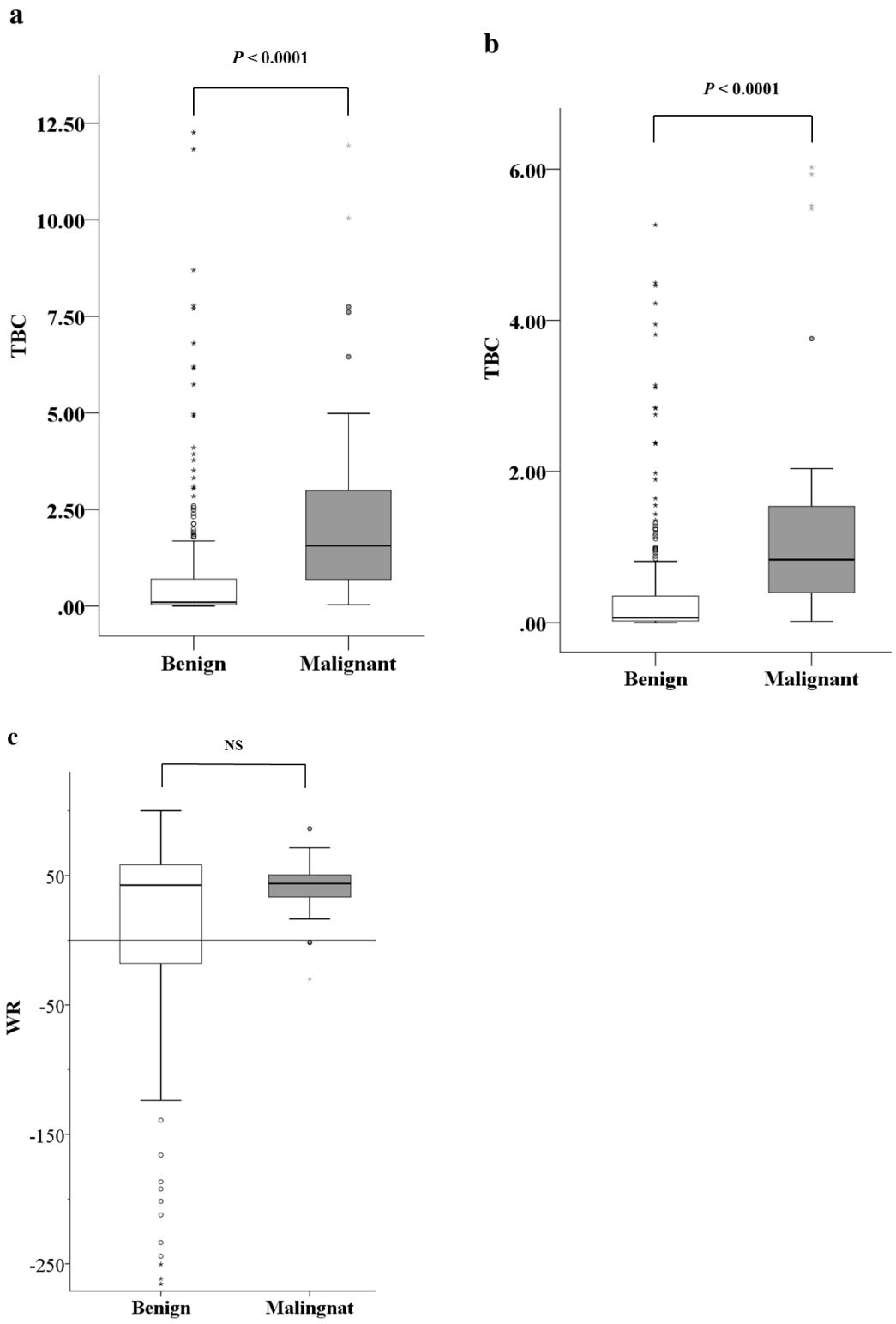


Fig. 3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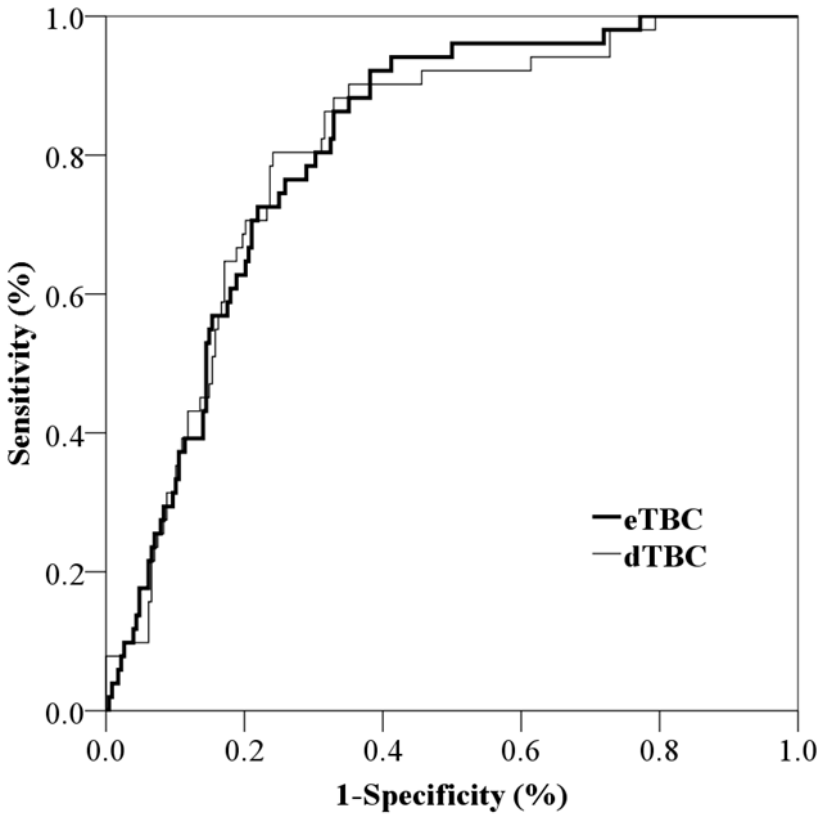
10.00
7.50
5.00
2.50
.00
TBC
Benign
Malignant
b
P < 0.0001
6.00
4.00
2.00
.00
TBC
Benign
Malignant
c
NS
50
-50
-150
-250
WR
Benign
Malingnat

Fig. 4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0.4
0.2
0.0
Sensitivity (%)
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1.0
1-Specificity (%)
eTBC
dTBC