RESEARCH PAPER

Prediction of pathological fracture in patients with lower limb bone metastasis using computed tomography imaging

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Abstract

Lower limb pathological fractures caused by bone metastases can severely impair activities of daily living, so recognizing fracture risk is essential. Medial cortical involvement (MCI) in the proximal femur has been demonstrated to affect bone strength in biomechanical studies, but it has not been investigated in real patients. Between 2012 and 2019, 161 bone metastases with computed tomography (CT) images were retrospectively examined. Twenty-nine fractures were observed including 14 metastases with pathological fractures at the first examination, and prophylactic surgery was performed for 50 metastases. We extracted clinicopathological data using CT images, including patient's background, MCI in the proximal femur, site, size, circumferential cortical involvement (CCI), pain, and nature of metastasis. Cox proportional hazard regression analyses were performed, and we created integer scores for predicting fractures. We revealed that MCI, CCI, lytic dominant lesion, and pain were significant factors by univariate analyses. By multivariable analysis, MCI and each 25% CCI were significant and integer score 1 was assigned based on hazard ratio. The full score was four points, with MCI in the proximal femur (one point) and $\geq 75\%$ CCI (three points). With integer score two, sensitivity was 88.9% and specificity was 81.2% for predicting fracture within 60 days. In conclusion, MCI and CCI examined by CT images were the risk factors for pathological fracture. CCI $\geq 50\%$ is a widely known risk factor, but in addition, it may be better to consider surgery if MCI in the proximal femur is observed in metastasis with 25–50% CCI.

Keywords Bone metastasis · Pathological fracture · Cortical involvement · Scoring system · Lower extremities · Femur

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Abbreviations

SREs	Skeletal related events
ADL	Activities of daily living
QOL	Quality of life
MCI	Medial cortical involvement
BMA	Bone-modifying agent
CT	Computed tomography
CRP	C reactive protein
Alb	Albumin
CCI	Circumferential cortical involvement
ROC	Receiver Operating Characteristic
AUC	Area under the curve
IQR	Interquartile range
HR	Hazard ratio
FE method	Finite element method

Introduction

The development of molecular-targeted drugs and immune-checkpoint inhibitors has contributed to better survival rates in advanced-stage cancers [1, 2]. Bone is the third most common site of metastasis, after the lungs and the liver [3, 4], and avoiding skeletal related events (SREs) is important for maintaining activities of daily living (ADL) and quality of life (QOL) [5, 6]. Particularly, lower limb fractures can severely impair ADL and QOL [5, 6]. In addition, prophylactic surgery for femur yielded better results than surgery for completed fractures with shorter hospital stay, greater likelihood of discharge to home, and greater walking ability [7].

To avoid pathological fractures, recognition of high-risk metastatic lesions is essential, while on the other hand, patients with a low risk of pathologic fractures should be spared overtreatment. Therefore, there have been many studies predicting pathological fractures. A representative study was performed by Mirels in 1989 [8], which reported site, nature, size, and pain as the prognostic factors for predicting fractures. Van der Linden reported cortical involvement is important in 2003 [9]. These factors were widely known and used for predicting pathological fractures.

There are several areas for improvement with regards predicting pathological fractures. First, medial cortical involvement (MCI) in the proximal femur has not been assessed, which is important for bone strength certified by biomechanical analysis [10–15]. Second, there have been fewer studies in recent years, despite the treatments for cancer having made much progress, including the introduction of bone modifying agents (BMA). Third, patients with a fracture at the first presentation, or patients with impending fracture who would receive surgery soon after the first presentation, might not be included into prospective analyses due to ethical problems in recent years. Forth, regarding the nature of the metastases, intertrabecular metastases have not been analyzed, and mixed lesions represent too wide a range of metastasis. Finally, many studies did not use computed tomography (CT) images for evaluating the pathological fracture risk, although it is routinely used for detecting systemic metastases, and is recommended for measuring the value of axial cortical involvement and other risk factors to further improve fracture risk prediction [16].

The purpose of this study is the re-evaluation of risk factors of pathological fracture in lower limb metastases. We included metastases with fracture or impending fracture, and investigated fracture risk by Cox proportional hazard regression analysis for considering time course. In addition to Mirels' classification, we explored factors associated with site, size, nature, and pain in detail and compared to Mirels' classification using only CT images. Then we aimed to construct a new scoring system for predicting pathological fractures.

Patients and methods

Study design

This retrospective study was conducted at two university hospitals and one cancer center in Japan.

Participants and data collection

The records of patients with lower limb bone metastasis who were consulted to an orthopedic surgeon in the three institutions between April 2012 and March 2019, were included in the study. In one university hospital and one cancer center, mainly patients with fracture, impending fracture, or pain were consulted to orthopedic surgeons. Meanwhile, in the other university hospital, which has a multidisciplinary team for the treatment of bone metastases, patient was consulted to an orthopaedic surgeon when bone metastasis was detected, even if fracture risk was low. Although the timing of consultation to orthopaedic surgeons were different, the treatment strategy and surgical indication for lower limb metastases in three institutions were same as shown in Fig. 1. Bone metastases were detected using CT, magnetic resonance imaging (MRI), Tc-99 m MDP bone scintigraphy, or fluorodeoxyglucose-positron emission tomography (FDG-PET). Ultrasound or CT-guided percutaneous biopsy was performed in cases of inconclusive lesions. Only bone metastases with CT images were included in this study. We also included patients who had a pathological fracture in the lower limb at the first examination.
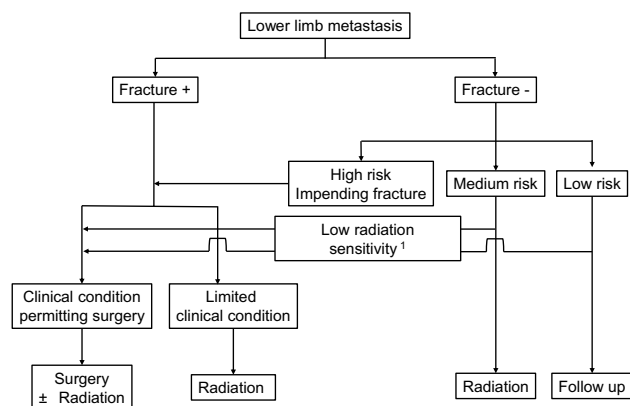

Fig. 1 Treatment strategy for lower limb bone metastases. [1] Tumor with low radiation sensitivity, indicates renal cell carcinoma, thyroid cancer, and hepatocellular carcinoma

We defined the day of CT scan covering lower limb metastasis as day zero. Then we defined the final follow-up date; for patients with fracture: the fracture date; for patients who underwent prophylactic surgery: the date of surgery; and for patients without fracture or surgery: the final follow-up date. For patients with fracture at first examination, the follow-up period was defined as zero (Supplementary Table 1).

We extracted the following clinicopathological data on day zero: age, sex, primary lesion, history of chemotherapy, history of BMA, history of local radiation therapy, laboratory data (serum C-reactive protein [CRP], and albumin [Alb]), and whether patients had pain (categorized to

Table 1 Baseline characteristics of patients (N = 154)

Variables	Number
Age, mean ± SD	65.7 ± 12.8
Gender, male, n (%)	77 (50.0)
Primary lesion, n (%)	
Lung cancer	36 (23.4)
NSC with molecular target therapy	6 (3.9)
Other lung cancer	30 (19.5)
Breast cancer	23 (14.2)
Hormone dependent	20 (13.0)
Hormone independent	3 (1.9)
Renal cell carcinoma	15 (9.7)
Prostate cancer	10 (6.5)
Hormone dependent	6 (3.9)
Hormone independent	4 (2.6)
Pancreatic cancer	8 (5.2)
Multiple Myeloma	7 (4.5)
Urothelial cancer	6 (3.9)
Gastric cancer	5 (3.2)
Hepatocellular carcinoma	5 (3.2)
Malignant Lymphoma	5 (3.2)
Thyroid cancer	4 (2.6)
Esophageal cancer	4 (2.6)
Sarcoma	4 (2.6)
Others	22 (14.3)
Primary lesion (Katagiri's classification), n (%)	
Slow growth	44 (28.6)
Moderate growth	42 (27.3)
Rapid growth	68 (44.2)
History of chemotherapy, n (%)	84 (54.5)
Induction of BMA, n (%)	
Before the baseline	13 (8.4)
After the baseline (during follow up)	50 (32.5)
Laboratory data	
CRP (mg/dl), mean ± SD (n = 159)	3.16 ± 5.23
Alb (g/dl), mean ± SD (n = 160)	3.55 ± 0.66

NSC non small cell lung cancer, *BMA* bone modifying agent

functional pain on weight-bearing, and other pain) caused by the metastasis. Primary lesions of the metastases were classified based on Katagiri's score [17]. Lung cancer was classified into two groups based on the presence of the Epidermal Growth Factor Receptor [EGFR] mutation or anaplastic lymphoma kinase [ALK] rearrangement. Prostate cancers were classified into hormone-sensitive and hormone-resistant groups. Breast cancers were classified into hormone-receptor positive and negative groups. We then examined whether patients had BMA administration, local radiation therapy, or surgery for lower limb metastasis during the follow-up period.

Next, we examined the metastasis using axial CT images and extracted the following data: site (peri-trochanteric lesion, or other lower limb skeleton), MCI in the proximal femur (yes or no), size according to Mirels' score (tumor/bone width < 1/3, 1/3–2/3, and > 2/3), CCI (< 25%, < 50%, < 75%, and ≥ 75%), and nature (five-tiered approach: intertrabecular, lytic, mixed [lytic dominant or blastic dominant], and blastic). We defined the proximal femur as the femoral head, femoral neck, intertrochanteric lesion, and femoral shaft proximal to the lower edge of the lesser trochanter. The medial cortex at the proximal femur was defined as thickened cortical bone at the medial neck or the antero-medial quarter of the femoral section anterior to the lesser trochanter (Fig. 2) [10, 11]. Cortical involvement was defined as any detectable change in the cortical bone by axial CT images. Intertrabecular metastasis was defined as those which made no detectable change in the cortical bone on CT images. With regards to nature, we made a two-tiered classification, which divided the nature into lytic dominant lesion (lytic and lytic dominant lesions in five-tiered classification) and others (blastic, blastic dominant, and intertrabecular). For Mirels' classification of nature, we categorized intertrabecular metastases into blastic lesion.

Analysis of fracture risk

The fracture risk was investigated using Cox proportional hazard regression analysis. We analyzed fracture risk by the patient's background and factors related to the metastasis itself. Site was classified by Mirels' classification or the existence of MCI in the proximal femur. Size was classified by Mirels' classification or CCI. Nature was classified by five-tiered, Mirels', or two-tiered classification. Pain was classified by Mirels' classification or the presence of pain (yes or no) including moderate and functional pain in Mirels' classification. Definition of event occurrence and censoring was shown in Supplementary Fig. 1. A *p*-value < 0.05 was regarded as statistically significant. Factors referred to the metastasis itself, with higher hazard ratio and lower *p*-value, were investigated by multivariable Cox proportional hazard
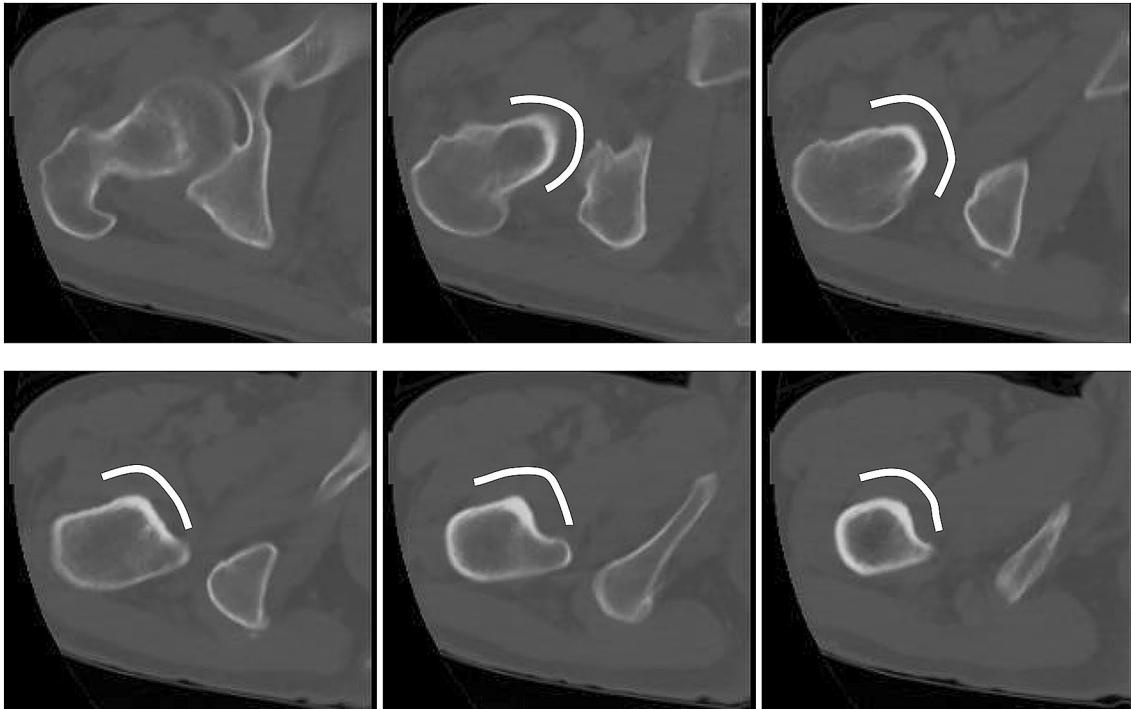
Fig. 2 Medial cortex in the proximal femur evaluated by CT axial images. Medial cortex at the proximal femur was defined as thickened cortical bone at the medial neck or the antero-medial quarter of the femoral section anterior to the lesser trochanter

regression analysis. The integer score was calculated by hazard ratio.

A survival curve assessing fracture risk was drawn by integer score using Kaplan–Meier method, and a Log-rank test was performed with reference to score 0–1. A receiver operating characteristic (ROC) curve was drawn using logistic regression analysis and area under the curve (AUC) was calculated. Inclusion and categorization of data was shown in Supplementary Table 2.

Statistical analysis

Statistical analyses were performed using JMP® 14 (SAS Institute Inc., Cary, NC, USA).

Results

Between April 2012 and March 2019, the number of patients with lower limb bone metastasis in our institutions was 172, and among them, local CT images were available in 154 patients, with 161 lower limb bone metastases.

Table 1 shows the baseline characteristics of the patients. Mean age was 65.7 years, and 50% of the patients were male. With regards to the primary lesion of the bone metastases, lung cancer was the most common, followed by breast cancer and renal cell carcinoma. According to Katagiri's

classification, 44.2% of the primary lesions were rapid growth tumors. BMA were used in 13 (8.4%) patients, and started administration during follow-up in 50 (32.5%) patients. Mean serum CRP was 3.16 mg/dL and Alb was 3.55 g/dL.

Supplementary Table 1 shows the frequency of the fracture and the follow-up period. Among the 161 metastases, fracture occurred in 29 metastases, including 14 metastases which had already fractured and were identified at the first examination. Fifteen patients fractured during follow-up with median interval of nine days (Interquartile range, IQR 4–40). All fractured patients underwent surgery for metastases. We performed prophylactic surgery for 50 metastases. Median follow-up period for metastases without fracture was 42.5 days (IQR 13–132). Median follow-up period across all patients was 33.0 days (IQR 10–115).

Table 2 shows the fracture risk based on Cox proportional hazard regression analysis. BMA administration, MCI at proximal femur, size, nature, and pain were significantly related to fracture risk.

With regards BMA, no fracture occurred in patients with BMA induction before CT evaluation. Patients with administration of BMA during follow-up had a significantly lower risk of fracture.

With respect to tumor size, metastases with larger ratio of tumor size/bone width had significantly higher risk with reference to size < 1/3. CCI was significantly related to fracture

Table 2 Fracture risk based on cox proportional hazard regression analysis (161 metastases, 29 fractures)

Variables	Number (%)	Hazard ratio	95%CI	*p value*
Systemic factors				
Age ≥ 70	64 (39.8)	1.07	0.51–2.24	0.86
Gender, Male	83 (51.6)	0.74	0.36–1.54	0.43
Primary lesion (Katagiri's classification)				
Slow growth	48 (29.8)	Ref		
Moderate growth	43 (26.7)	1.30	0.53–3.21	0.57
Rapid growth	70 (43.5)	0.72	0.29–.77	0.47
History of chemotherapy	91 (53.8)	0.78	0.38–1.60	0.50
Induction of BMA				
Before baseline[†]	13 (8.1)	1.8×10^{-9}	-	1.00
Before baseline and during follow up	65 (40.4)	0.14	0.04–0.46	0.001**
Laboratory data				
CRP ≥ 3.0 (mg/dl) (n = 159)	51 (32.1)	0.81	0.36–1.83	0.61
Alb < 3.0 (g/dl) (n = 160)	31 (19.4)	0.87	0.33–2.29	0.78
Local factors				
Site				
Mirels' classification				
Other lower limb (score 2)	48 (29.8)	Ref		
Peritrochanter (score 3)	113 (70.2)	2.71	0.94–7.80	0.06
Medial cortical involvement at proximal femur	59 (36.6)	4.94	2.24–10.9	< 0.0001**
Size				
Mirels' classification (Tumor size / bone width) (n = 160)				
< 1/3 (score 1)	34 (21.4)	Ref		
1/3–2/3 (socre 2)	38 (23.9)	1.62	1.01–2.61	0.046*
> 2/3 (score 3)	87 (54.7)	1.66	1.08–2.56	0.02*
Circumferential cortical involvement				
< 25%	85 (52.8)	Ref		
< 50%	32 (19.9)	23.7	2.82–198	0.004**
< 75%	17 (10.6)	31.3	3.46–282	0.002**
≥ 75%	27 (16.8)	127.4	16.5–987	< 0.0001**
Nature				
5 Tiered classification				
Intertrabecullar	23 (14.3)	Ref		
Blastic	16 (9.9)	1.41	0.09–22.5	0.81
Blastic dominant	20 (12.4)	2.53	0.23–28.0	0.45
Lytic dominant	42 (26.1)	6.09	0.77–48.2	0.09
Lytic	60 (37.3)	7.73	1.02–58.5	0.048*
Mirels' classification				

Table 2 (continued)

Variables	Number (%)	Hazard ratio	95%CI	*p value*
Blastic (including intertrabecullar type) (score 1)	47 (28.0)	Ref		
Mixed (score 2)	64 (38.1)	2.22	0.70–6.98	0.17
Lytic (score 3)	57 (33.9)	3.24	1.06–9.88	0.04*
2 Tiered classification (lytic dominant and others)				
Lytic dominat (lytic and lytic dominant in 5 tier)	109 (64.9)	5.83	1.76–19.3	0.004**
Pain (n = 160)				
Mirels' classification				
Mild (score 1)	71 (44.4)	Ref		
Moderate (score 2)	46 (28.8)	6.23	2.27–17.1	0.0004**
Functional (score 3)	43 (26.9)	3.19	1.04–9.80	0.04*
Presence of pain (score 2 and 3 in Mirels')	89 (55.6)	4.72	1.79–12.5	0.002**
Local radiation therapy				
Past history (n = 159)	4 (2.5)	3.40	0.80–14.5	0.10
During follow up (n = 160)	24 (15.0)	1.04	0.40–2.73	0.94

CI confidence interval, * p < 0.05; ** p < 0.01, † no fracture occurred

risk and hazard ratio (HR) increased as the involvement area increased.

Regarding the nature of the metastasis, fracture risk was significantly higher only on lytic metastasis in five-tiered classification (HR, 7.73; *p* = 0.048) with reference to intertrabecular metastases. Fracture risk on blastic metastasis was not significantly lower compared to that on intertrabecular metastasis. In Mirels' classification, mixed and lytic lesions had significantly higher risk of fracture (HR, 2.22 and 3.24, respectively). Fracture risk was significantly high in lytic dominant lesions (HR, 5.83; *p* = 0.004) by two-tiered classification.

When pain was classified according to Mirels' classification, metastases with moderate pain (HR, 6.23; *p* = 0.0004) and functional pain (HR, 3.19; *p* = 0.04) had higher risk compared to those with mild pain, but the hazard ratio was not increased as the score increased. Meanwhile, metastases with any pain had higher fracture risk (HR, 4.72; *p* = 0.002) compared to those without pain.

Table 3 shows the results of the multivariable analysis of fracture risk. MCI at the proximal femur (HR, 2.35; *p* = 0.03) and CCI (unit HR, 3.13; *p* < 0.0001) were significantly

related to fracture. We assigned the integer score 1 to MCI in the proximal femur and each 25% CCI. The full score was four points, with MCI in the proximal femur (one point) and ≥ 75% CCI (three points). The number of patients with integer score 0 point was 70, 1 point: 32, 2 points:18, 3 points:26, and 4 points:15.

Figure 3 shows the survival curve assessing fracture risk with prognostic scores calculated by the integer score by Kaplan–Meier method. The survival rate of score 2, 3, and 4 was each significantly different from that of score 0–1.

Figure 4a shows the ROC curve created based on metastases with fracture within 60 days and those without fracture over 60 days (n = 114). The AUC was 0.924 for new prognostic score and 0.827 for Mirels' score. With integer score 2, sensitivity was 88.9% and specificity was 81.2%. Figure 4b shows the ROC curve created by metastases excluding those with fractures at the first examination. The AUC was 0.878 for the new score and 0.843 for Mirels' score.

Table 4 shows the fracture risk by prognostic score. The Fracture risk in 60 days was 8.0% with a score of 1, 28.0% with a score of 2, 63.4% with a score of 3, and 88.6% with a score of 4.

Table 3 Multivariable analysis of fracture risk of bone metastases. (161 metastases, 29 fractures)

Variables	Hazard ratio	95%CI	p	Integer score	Range
Medial cortical involvement at proximal femur	2.35	1.06–5.22	0.03*	1	0–1
Circumferential cortical involvement (CCI)	3.13[†]	2.10–4.91	< 0.0001**	1[‡]	0–3
Lytic dominat or not	1.59	0.45–5.61	0.47		
Presence of pain	1.17	0.43–3.19	0.77		

CI conficence interval, * p < 0.05; ** p < 0.01

[†]Calculated by unit risk ratio for 25% involvement

[‡]Integer score of CCI < 25%: 0, < 50%: 1, < 75%: 2, ≥ 75%: 3
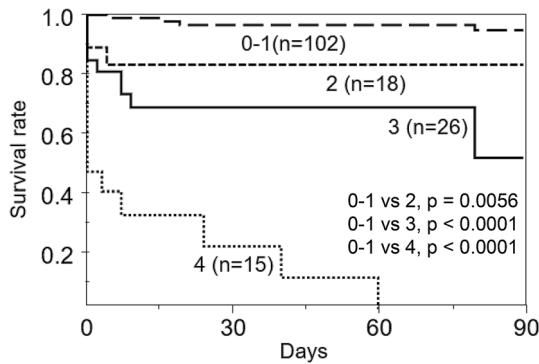
Fig. 3 Fracture risk classified by the prognostic score (Kaplan–Meier method)

Discussion

We retrospectively analyzed the risk factors of pathological fractures in lower limb metastases using CT images. Twenty-nine metastases fractured among 161 metastases, and BMA administration, MCI at the proximal femur, CCI, lytic dominant lesions (two-tiered classification), and presence of pain were significantly related to pathological fracture by univariate Cox proportional hazard regression analysis. In the multivariable analysis, among factors related to the local lesion, MCI and 25% each CCI was significantly related. We constructed a scoring system to predict pathological fractures by assigning an integer score 1 to both. A Full score was four points with ≥ 75% CCI, and MCI in the proximal femur. We plotted a ROC curve investigating 60-days fracture risk and the AUC was 0.924. With integer score 2, sensitivity was 88.9% and specificity was 81.2% for pathological fractures.

In this study, we included metastases with fractures or impending fractures which might have the highest risk of fracture. For the last two decades, there have been studies analyzing the fracture risk after radiation therapy, but it might be possible these studies did not include metastases at high risk. In many institutions in Japan, prophylactic surgery may treat impending fractures, soon after the first
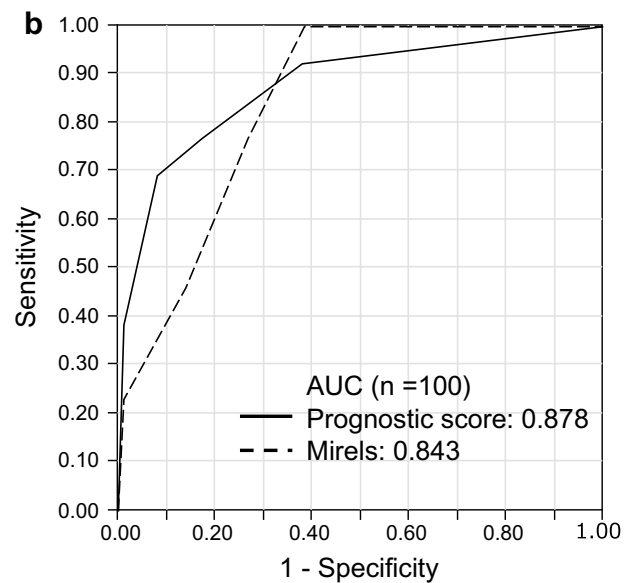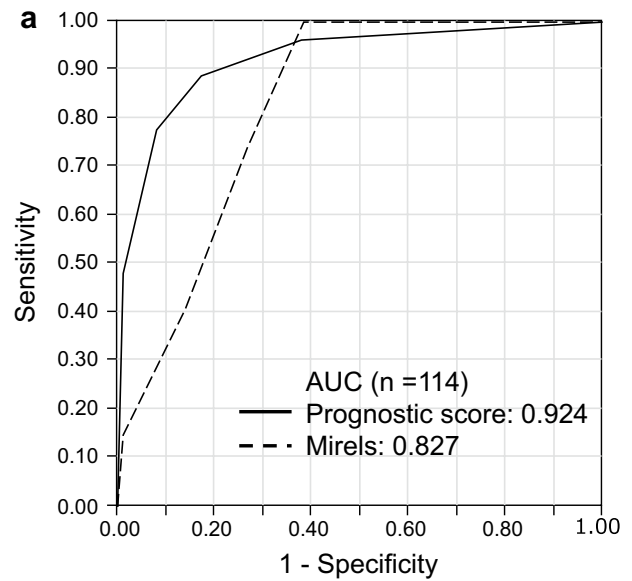

Fig. 4 60-day fracture risk by the prognostic score and Mirels' score. **a** All cases following 60 days, **b** metastases with fracture at the first examination was excluded

Table 4 Fracture risk by the prognostic score (%)

Follow up period (day)	30	60	90
Metastasis (n)	124	114	107
Fracture (n)	25	27	29
Prognostic score			
0	2.2	1.9	2.7
1	7.7	8.0	10.6
2	24.0	28.0	33.3
3	54.2	63.4	67.8
4	81.6	88.6	89.9

examination and these metastases might not be included in these studies. As the analysis of high-risk metastases are important for investigating the risk factors of fracture, we included metastases with fracture and impending fracture, and analyzed by Cox proportional hazard regression methods taking time course into account. Meanwhile, we also included many patients with metastases at low risk of fracture who were consulted to a multidisciplinary team soon after the diagnosis of bone metastasis. As a result, we included metastases with a wide range of fracture risks (Fig. 3).

In the present study, we focused on MCI in the proximal femur, and showed that any detectable change to the lesion on CT images increased the risk of fracture. Keyak et. al. first described defects of the medial cortex highly affecting the bone strength using finite element (FE) methods [10]. Many studies have shown the defect at the lesion was the risk factor for pathological fracture using FE methods or biomechanical analyses [11–15]. However, there has been no study which examined the risk of MCI in the proximal femur compared with other risk factors. This is the first study to demonstrate that involvement of the lesion was a significant risk factor in multivariable analysis.

With regards the nature of the metastases, many studies have analyzed the risk by classifying metastases into lytic, blastic, and mixed lesions. However, in reality, there are many intertrabecular metastases [18, 19]. We defined intertrabecular metastases as those which made no detectable change in the cortical bone on CT images. In addition, conventional mixed lesions have a very wide range of images, thus, we divided the mixed lesions into lytic dominant and blastic dominant. As a result, we constructed a five-tiered classification including intertrabecular metastases. As there has been no study investigating the mechanical strength of intertrabecular metastases, we analyzed the risk of fracture, and showed the fracture risk of intertrabecular metastases might be low compared with that of other metastases, although not significant. Our results showed the hazard ratio of 5-tiered classification was increased as the lytic factor increased, although not significantly so due to the small

sample size. This showed the potential usefulness of this classification. We then constructed a 2-tiered classification: lytic dominant (lytic and lytic dominant in 5-tiered classification), and others (blastic dominant, blastic, and intertrabecular type). In the present study, this classification was of most use when predicting the fracture risk. In this classification, the hazard ratio for lytic dominant lesions was 5.83 with a p-value < 0.004, but it was not significant in the multivariable analysis.

Pain is reported as a risk factor of pathological fracture. Mirels classified the pain into mild, moderate, and functional pain, but our results showed the hazard ratio of moderate pain was higher than that of functional pain. Thus, we classified the pain into two groups: metastases with pain, or without pain. This classification is quite simple and useful, however it was not significant in the multivariable analysis. Although several studies reported increased pain was the risk factor [20], and prophylactic internal fixation was recommended in cases of increasing pain [21], we could not examine this because our study was retrospective. Pain has been shown to be related to fracture to some extent, but despite patients not complaining of pain, fracture might occur. We showed that early detection of bone metastasis from hepatocellular carcinoma before the symptoms arise might lead to prevention of pathological fracture or paralysis [22]. Therefore, caution to not miss asymptomatic metastases in patient should be taken, particularly with impending fracture or paralysis, when consulted by the oncologist.

The most influential risk factor of pathological fracture reported is cortical involvement. The oldest study found on this topic was published in 1981 [23]. Based on plain radiographs, the author estimated the percentage of metastatic circumferential involvement by dividing them roughly into four categories of cortex involved: less than 25%, 25–50%, 50–75%, and over 75%. It was concluded that metastatic long bones involving over 50% of the cortex were likely to fracture and should be considered for prophylactic fixation. Cortical destruction or involvement ≥ 50% has been reported as a risk factor in other studies using plain radiographs [9, 20, 24]. However, error ranges may be wide for predicting the cortical involvement from plain radiographs, thus we used CT as our imaging modality. There was a report, using CT images, that cortical involvement ≥ 30% was a risk factor [25]. In the present study, fracture risk at 60 days with integer score 2 was 28.0% (Table 4), which was considered high risk. Therefore, if cortical involvement is 25–50% with involvement of the medial cortex in the proximal femur, or if cortical involvement is over 50%, surgery may have to be considered, regardless of pain or nature.

In the present study, excluding patients with fracture at the first examination, we performed surgery on 12.7% of zero points, 48.4% of one point, and 81.1% of 2–4 points metastases (data not shown). It is imperative to avoid

overtreatment for metastases, because surgical overtreatment also unnecessarily increases morbidity (e.g., hospitalization, general anesthetics, and complications arising from a forced supine position) in patients whose life expectancy is already limited [25]. However, the reason we performed surgery for lower risk metastases might be the sensitivity to radiation therapy as shown in our strategy (Fig. 1). If the sensitivity to radiation and systemic therapy was low, metastases might increase and involve the cortex soon, which leads to fracture. Therefore, in addition to this scoring system, we should consider increasing speed and sensitivity for systemic therapy or radiation therapy for deciding surgical indications.

By univariate analysis, BMA administration was significantly related to fractures among systemic factors. We included BMA into the analyses because BMA has been reported to reduce fracture risk in many studies. However, we did not include BMA in the multivariate analysis in the present study, because the follow-up period was too short to see the effect, and BMA administration may have a large selection bias. As shown in Fig. 1, if the metastasis is fractured or at high risk, we perform surgery as soon as possible, and generally we administrate BMA after surgery. On the other hand, if we decide not to perform surgery, we will initiate BMA. Therefore, in the follow-up period in this study, we used BMA only on patients with medium or low risk of fracture, which created the selection bias. When we start BMA, we have recognized the metastases and taken care not to fracture. We perform prophylactic surgery if needed, which leads to a low rate of fracture occurrence in the BMA administrated group, in retrospective studies such as this. In the present study, indeed, no fracture occurred in 14 patients who had been administered BMA before the follow-up period. In other words, detecting metastases at low or medium risk may be important for preventing fractures.

In the same way, radiation therapy may have large selection bias in this study. We gave priority to surgery when the metastasis was at high risk of fracture, because radiation therapy is proven not to be significantly effective for preventing fracture [26]. We only performed radiation therapy to metastases at medium risk, or in the case that we had to wait for surgery for metastases at high risk for various reasons.

The present study has some limitations. First, this is a retrospective study, and included metastases with fractures at the first presentation for analyzing metastases with higher risk. When we examined CT images after fracture, we could not measure the exact size of the tumor or exact range of cortical involvement. However, we could not perform a prospective study because we cannot wait and see the impending fracture till fracture occurs. In addition, some risk factors for fracture could not be included, such as assistant devices, weight-bearing status, bone density status, smoking status,

and osteoporosis comorbidity in addition to BMA administration and local radiation therapy. Second, we did not confirm the pathology of metastases.

In conclusion, MCI in the proximal femur and CCI examined by CT images were the risk factors for pathological fracture. CCI ≥ 50% is a widely known risk factor, but in addition, it may be better to consider surgery if the MCI in the proximal femur is observed in metastasis with 25–50% CCI.

Compliance with ethical standards

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