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FULL PAPER

Effect of Bone Reading CT software on radiologist performance in detecting bone metastases from breast cancer

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Objective: To evaluate the effect of CT software that generates rib unfolding images and automatically numbers ribs and thoracic spines on radiologist performance in detecting thoracic bone metastases from breast cancer.

Methods: A total of 126 patients with breast cancer who underwent chest CT and fludeoxyglucose (FDG)-positron emission tomography (PET)/CT and/or bone scans were retrospectively reviewed. One board-certified radiologist (R1) and one radiology resident (R2) independently assessed the original chest CT and rib unfolding images using a commercially available post-processing software (Bone Reading) application to evaluate metastasis in the ribs and thoracic spines. Results were compared with reference standard based on CT, FDG-PET/CT and/or bone scan with follow-up.

Results: Based on reference standard, 78 metastatic bone lesions in 26 patients were identified. On per-patient-based analysis, Bone Reading assessed by R1/R2 had a sensitivity of 84.6%/80.8% and a specificity of 94.0%/94.0% with an accuracy of 92.1%/91.3%. The original CT reading yielded a sensitivity of 73.1%/57.7% and a specificity of 95.0%/94.0% with an accuracy of 90.5%/86.5%. The sensitivity and accuracy of Bone Reading were significantly higher than those of CT reading, as assessed by R2 (both $p = 0.031$). On per-lesion-based analysis,

Bone Reading assessed by R1/R2 yielded a sensitivity of 84.6%/82.1% and a specificity of 99.7%/99.6% with an accuracy of 99.4%/99.3%, while the original CT reading yielded a sensitivity of 71.8%/62.8% and a specificity of 99.6%/99.5% with an accuracy of 99.2%/98.9%. The sensitivity and accuracy with Bone Reading application were significantly higher than those with CT reading by both readers (R1, $p = 0.006$ and $p = 0.036$, respectively; R2, both $p < 0.001$). The mean reading time needed for Bone Reading application was significantly shorter than that for original chest CT reading ($p < 0.001$). Bone Reading application helped readers find small and sclerotic lesions missed in original CT reading.

Conclusion: In patients with breast cancer, the use of Bone Reading application improved radiologist performance in bone metastasis detection compared with original chest CT reading with reduced reading time. This software will be more helpful to inexperienced radiologists for improving the reading performance.

Advances in knowledge: Small and sclerotic lesions can be easily missed in original CT reading. Using Bone Reading CT software can enhance the performance of radiologists in detecting bone metastasis in breast cancer. False-negative rates can be significantly reduced in both inexperienced and experienced readers.

INTRODUCTION

Breast cancer is the most common cancer in females with an annual incidence of 1.8 million worldwide.¹ Bone is the most common site of distant metastasis in breast cancer with an incidence rate of 73% in post-mortem examination.² Bone metastases cause serious complications such as pain, hypercalcaemia, pathologic fracture and spinal cord compression. As life expectancy of breast cancer increases, early detection of bone metastasis and timely therapy are important to improve the quality of life of patients.

Common locations of bone metastases from breast cancer include the ribs, sternum and spines of the thoracic cage.³ Therefore, earnest attention is needed to detect bone metastases in chest CT of patients with breast cancer.

Breast cancer is one of the malignant diseases in which CT scans are commonly used to evaluate the presence or absence of metastasis. The authors had frequently experienced overlooking of bone metastasis in the chest CT reading, but the lesion was detected later retrospectively

after performing a bone scan or positron emission tomography (PET)/CT, and this occurred more frequently in breast cancer than in other malignancies such as lung cancer. Recently, we applied a software called “Bone Reading” that could display rib unfolding images and automatically number ribs and spines for bone evaluation in chest CT of breast cancer. The performance and usefulness of this software have been demonstrated in

trauma and a few oncology patient groups.⁴⁻⁷ However, to the best of our knowledge, the effect of this software on radiologist performance with different experience levels in breast cancer has not been reported yet.

The objective of this study was to evaluate the effect of Bone Reading CT software on the performance of radiologists who

Figure 1. Screenshot of the Bone Reading application showing the display configuration in a 65-year-old female patient: (a) an unfolded rib image. Ribs are rotatable by scrolling the mouse or clicking icons under the image. When the reader clicks a region of interest in the unfolding image (arrowheads), the position is marked in sagittal (b), coronal (c), transverse (d) and perpendicular to the rib centreline planes (e) simultaneously. Sagittal and coronal images of T-spines (f, g) are shown as one view. Zoomed transverse image (h) of the same point with sagittal and coronal images is also available. The automatically numbered ribs and vertebrae can be noted.

had different experience levels in detecting bone metastases from breast cancer.

METHODS AND MATERIALS

Subjects

Our institutional ethical committee approved this retrospective study. The requirement for informed consent was waived. A total of 140 consecutive patients diagnosed with breast cancer, who underwent chest CT, fluorine-18 fludeoxyglucose (^{18}F -FDG)-PET/CT and/or bone scan from August 2014 to March 2015, were enrolled. 14 patients were excluded owing to loss to follow-up ($n = 11$) or equivocal standard of reference ($n = 3$). Finally, a total of 126 patients were included in this study, including 105 patients who had invasive ductal cell carcinoma, 19 patients who had invasive lobular carcinoma and 2 patients who had the mixed type. All 126 patients were confirmed to have breast cancer *via* surgery or biopsy and clinical follow-up. Chest CT, ^{18}F -FDG-PET/CT and/or bone scan were performed within an interval of 1 month, which was part of the routine protocol for staging or evaluating metastases at follow-up for patients with breast cancer at our institution.

Imaging techniques

CT imaging data acquisition

CT scans were performed with one of two different CT systems (Ingenuity, Philips Medical Systems, Netherlands; Somatom Flash; Siemens Healthcare, Forchheim, Germany) using a 128 multidetector CT unit. Scanning was performed from the level of the thoracic inlet to the level of the middle portion of kidneys. Contrast agent (Iohexol, 350 mg ml^{-1} , Omnipaque™ GE Healthcare) was applied at dose adjusted to body weight at an injection speed of $2\text{--}3\text{ ml s}^{-1}$ *via* the antecubital vein. Two sets of image acquisition parameters were used, as shown in the following: (a) 120 kVp, 150–250 mA, $128 \times 0.67\text{-mm}$ detector collimation, 0.7 beam pitch, 0.5-s gantry rotation time and reconstruction slice thickness 2 mm using a soft-tissue kernel and (b) 120 kVp, 150–200 mA, $128 \times 0.625\text{-mm}$ detector collimation, 1.0 beam pitch, 0.33-s gantry rotation time and reconstruction slice thickness 2 mm using a soft-tissue kernel. Axial data were also reconstructed with 2-mm-thick sections at 2-mm intervals for sagittal and coronal reformation.

Post-processing procedures

The 2-mm-based unfolding rib reformates were obtained using commercially available CT software “Bone Reading” (Syngo.via CT Bone Reading; Siemens Healthcare, Forchheim, Germany) (Figure 1). This software could provide unfolded rib and spine

views as a single layer. In the unfolded images, ribs were rotatable by mouse scrolling. Images were also available as multiplanar reformation in sagittal, coronal, transverse or perpendicular view to the rib central line. Sagittal and coronal views of thoracic spines showed all thoracic spines as one view. Zoomed transverse images of the same point with sagittal and coronal images were also available. Moreover, ribs and vertebrae were numbered automatically. All displayed images could be synchronized to the same location by simply clicking the mouse at a desired point.

Reference standard

One nuclear medicine specialist and one board-certified chest radiologist, who did not participate in image interpretation, performed the final confirmation of bone metastases, based on CT, ^{18}F -FDG-PET/CT and/or bone scintigraphy, and follow-up examinations, by consensus. Patients for whom the two readers could not reach consensus were excluded. The average follow-up time of the patients included in the study group was 14 months.

Imaging interpretation

The two radiologists, a board-certified chest radiologist with over 15 years' experience (R1) and a second-year radiology resident (R2), independently interpreted both chest CT scan and Bone Reading images on a workstation (Syngo.via; Siemens Healthcare). Before the reading process, the two readers received basic training in using the software algorithm and reviewed five cases that were not included in the study group. Both readers interpreted original chest CT scans first followed by Bone Reading. Time interval was 2 weeks between the two reading sessions. Both ribs and thoracic spines were subjected to analysis. The lower cervical and upper lumbar spines were excluded from analysis. When evaluating the original chest CT, both readers used axial, sagittal and coronal images for the detection and verification of lesions. Images were evaluated in bone window (width, 2000 HU; level, 500 HU). They were allowed to adjust parameters of window width and level. Both readers were required to record the location size, and the characters of the lesion. Lesion size was defined as the longest diameter of the lesion regardless of its shape. For the characters of the lesion, high-attenuation lesions on CT images were classified as sclerotic, low-attenuation lesions were classified as osteolytic and lesions with substantial sclerotic and osteolytic components were classified as mixed type. Reading time for each CT analysis was recorded synchronously. Measurement of reading time did not include loading or post-processing time of Bone Reading program because such processes were automatically performed at one time by assigning specific data sets to post-processing

Table 1. Location, number, size and character of metastatic bone lesions in patients with breast cancer

Location	Number	Mean size (range, mm)	Sclerotic	Lytic	Mixed
Left rib	29	25.6 (8–45)	17	12	0
Right rib	29	27.1 (6–47)	16	11	2
T-spine	20	32.9 (9–49)	13	4	3
Total	78	28.1 (6–49)	46 (59%)	27 (34.6%)	5 (6.4%)

Table 2. Analysis of bone metastasis on per-patient basis

Reader	Diagnostic Test	Chest CT	Bone Reading	<i>p</i> -value
R1	Sensitivity	73.1% (19/26)	84.6% (22/26)	0.250
	Specificity	95.0% (95/100)	94.0% (94/100)	1.0
	Accuracy	90.5% (114/126)	92.1% (116/126)	0.625
	False negative	26.9% (7/26)	15.4% (4/26)	0.250
	False positive	5% (5/100)	6% (6/100)	1.0
R2	Sensitivity	57.7% (15/26)	80.8% (21/26)	0.031
	Specificity	94.0% (94/100)	94.0% (94/100)	1.0
	Accuracy	86.5% (109/126)	91.3% (115/126)	0.031
	False negative	42.3% (11/26)	19.2% (5/26)	0.031
	False positive	6% (6/100)	6% (6/100)	1.0

R1, a board-certified chest radiologist with over 15 years' experience; R2, a second-year radiology resident. Significant differences were considered at *p*-value <0.05.

routine. When there were multiple lesions in the same anatomical location, only the largest one was recorded and considered for the interpretation of results. Negative findings included radiological benign lesions such as a callus formation of old fracture, bone island and degenerative changes. Results were compared with reference standard.

Statistical analysis

Statistical analysis was performed using SPSS® v. 22.0 statistical software (IBM Corp., New York, NY; formerly SPSS Inc., Chicago, IL). Sensitivity, specificity and accuracy were calculated for both readers. The McNemar's test was performed to compare the results of original CT reading and Bone Reading. The difference in reading time required for Bone Reading interpretation and original chest CT reading was evaluated by Student's paired *t*-test. A *p*-value of <0.05 was considered statistically significant. Interobserver correlation between CT scan and Bone Reading interpretation was tested with weighted kappa (*k*).

RESULTS

Patient population and lesion characteristics

Bone Reading software application was successfully processed for all 126 patients. In 26 (20.6%) of 126 patients, 78 skeletal metastases were identified using reference standard. Among the 26 patients, 14 patients had 1 lesion, 4 patients had 2 lesions, 2 patients had 3 lesions and the remaining 6 patients each had 5, 6, 7, 9, 10 and 13 lesions, respectively. Among the 78 metastatic lesions, 58 lesions were in the ribs (right ribs, *n* = 29; left ribs, *n* = 29), while 20 lesions were in thoracic spines. Of the 78 metastatic lesions, 46 (59%) metastatic lesions were sclerotic, 27 (34.6%) lesions were lytic and 5 (6.4%) lesions were mixed type. The mean size of lesions was 28.1 mm (range, 6–49 mm). Lesion distribution, size and characteristics are summarized in Table 1.

CT reading results on per-patient basis

Of the 26 patients with bone metastases, correct diagnosis was made for 19 patients by R1 (board-certified chest radiologist)

Table 3. Analysis of bone metastasis on per-lesion basis

Reader	Diagnostic Test	Chest CT	Bone Reading	<i>p</i> -value
R1	Sensitivity	71.8% (56/78)	84.6% (66/78)	0.006
	Specificity	99.6% (4442/4458)	99.7% (4444/4458)	0.804
	Accuracy	99.2% (4498/4536)	99.4% (4510/4536)	0.036
	False negative	28.2% (22/78)	15.4% (12/78)	0.006
	False positive	0.4% (16/4458)	0.3% (14/4458)	0.804
R2	Sensitivity	62.8% (49/78)	82.1% (64/78)	<0.001
	Specificity	99.5% (4436/4458)	99.6% (4441/4458)	0.332
	Accuracy	98.9% (4486/4536)	99.3% (4505/4536)	<0.001
	False negative	37.2% (29/78)	17.9% (14/78)	<0.001
	False positive	0.5% (22/4536)	0.4% (17/4458)	0.332

R1, a board-certified chest radiologist with over 15 years' experience; R2, a second-year radiology resident. Significant differences were considered at *p*-value <0.05.

and 15 patients by R2 (radiology resident) based on chest CT scan reading. With Bone Reading, correct diagnosis was made for 22 patients by R1 (board-certified chest radiologist) and 21 patients by R2 (radiology resident). The original CT reading by R1/R2 yielded a sensitivity of 73.1%/57.7%, a specificity of 95.0%/94.0% and an accuracy of 90.5%/86.5%. Bone Reading analysis by R1/R2 yielded a sensitivity of 84.6%/80.8%, a specificity of 94.0%/94.0% and an accuracy of 92.1%/91.3% (Table 2). There was improvement in sensitivity and accuracy for both readers through Bone Reading compared with CT scan reading. However, such improvement in sensitivity and accuracy was significant only for R2 (both $p = 0.031$). The false-negative rate was significantly ($p = 0.031$) reduced for R2.

CT reading results on per-lesion base

Among 78 metastatic lesions identified using reference standard, 56 lesions were correctly identified by R1, while 49 lesions were correctly identified by R2 based on chest CT scans. Through Bone Reading, 66 and 64 lesions were correctly identified by R1

and R2, respectively. Bone Reading performed by R1/R2 yielded a sensitivity of 84.6%/82.1%, a specificity of 99.7%/99.6% and an accuracy of 99.4%/98.3%. Original CT scan reading performed by R1/R2 yielded a sensitivity of 71.8%/62.8%, a specificity of 99.6%/99.5% and an accuracy of 99.2%/98.9% (Table 3). Lesion-based results regarding the specificity between chest CT scan and Bone Reading did not have significant differences. However, the differences in sensitivity and accuracy were significant for both readers (R1, $p = 0.006$ and $p = 0.036$, respectively; R2, both $p < 0.001$). The false-negative rate was significantly reduced for both readers ($p = 0.006$ for R1, $p < 0.001$ for R2).

Through Bone Reading, the two readers detected a total of 17 lesions which were missed in the original CT reading, including 11 lesions missed by R1 and 16 lesions missed by R2 (both readers commonly missed 10 lesions) in the original CT reading. The mean size of the 17 lesions was 15.9 mm (range, 6–40 mm), which was smaller than the mean size of 31 mm of the other 61 lesions.

Figure 2. A 42-year-old female patient who underwent left mastectomy owing to breast cancer: (a) the axial chest CT image showing a sclerotic lesion in the posterior arc of the left ninth rib (arrow) which was missed by the radiology resident. (b) Focal sclerotic lesion was detected in the rib unfolded image (short arrows). (c) Bone scan showing a focal linear uptake in the same location (arrow). (d) Fluorine-18 fludeoxyglucose (FDG) positron emission tomography/CT taken 1 month later showing FDG uptake in the liver (back arrow) and the rib (white arrow).

Of the 17 lesions, 13 lesions were sclerotic, 3 were lytic and 1 lesion was mixed in character (Figures 2 and 3). A total of 13 lesions were in the ribs, while 4 lesions were in the thoracic spines. 9 of these 13 lesions located in the ribs were found in the upper 1st–4th ribs. One of the four lesions found in the thoracic spine was located in the posterior element, while the other three lesions were located in the vertebral body (Figure 4).

Reading time

The mean reading time required for Bone Reading (R1, 57.2 ± 23.5 s; R2, 84.7 ± 23.1 s) was significantly ($p < 0.001$) shorter than that required for original chest CT reading (R1, 154.9 ± 43.3 s; R2, 183.9 ± 43.3 s) (Table 4).

Interobserver agreement

Interobserver agreement through Bone Reading was improved compared with that through original CT scan reading. In per-patient base analysis, the weighted kappa (k) value was 0.865 in CT reading and 0.930 in Bone Reading. On per-lesion basis, the weighted kappa (k) value was 0.893 in CT reading and 0.943 in Bone Reading.

DISCUSSION

With persistent trend of image data overload and increasing workload of radiologists, attempts have been made to improve the efficiency and accuracy of radiological reading process using advanced software algorithms.^{8–12} Bone Reading CT software used in our study could summarize the entire thoracic cage into a single plane and automatically number spines and ribs. Because ribs show complex shape with twisting course across many slices, small lesions can be easily missed on axial or planar images. Spine metastases involving only the bone marrow,

endplate or posterior element are difficult to be detected on CT. Moreover, numbering ribs and thoracic spines in chest CT is time consuming and exhausting. In this study, after using Bone Reading software, the detection rate was improved in both experienced and inexperienced radiologists. The improvement was more obvious for the inexperienced radiologist whose diagnostic accuracy reached the level of the experienced radiologist. The reading time required by both readers was also reduced, similar to the findings of other studies using this software for bone lesion detection.^{4–6}

In daily practice, breast cancer is one of most common malignant diseases for which chest CT scans are performed for the evaluation of metastasis. Readers can overlook metastatic bone lesions on CT scan when the evident bone destruction or soft-tissue formation is not accompanied.¹³ When slow-growing breast cancer cells infiltrate the bone marrow, they cause minimal osteoblastic responses, and owing to these responses small sclerotic lesions are formed.^{14,15} Sclerotic metastases are relatively acellular with lower volume of tumour tissues and less bone destruction than lytic lesions.^{16,17} The sensitivity of lesion detection by the radiology resident was 57.7% on patient-based analysis through original CT reading. The reason for such low sensitivity was that the inexperienced radiologist often missed patients with single metastatic bone lesion on CT, especially when the lesion was small and sclerotic. Missing such lesions in patients with single bone lesion directly affected the low sensitivity of detection on per-patient analysis. Bone Reading CT software enabled the readers to find more lesions which were small, sclerotic or in the upper ribs (1st–4th) than those in the original CT reading. Lesions in upper ribs might be more easily missed on CT reading than those in lower ribs because the

Figure 3. A 79-year-old female patient with right breast cancer: (a) the axial chest CT image showing a mixed lesion in the right first rib (arrow) which was missed by both readers in the original CT reading. (b) Coronal reformatted image of chest CT showing a mixed lesion in the eighth thoracic vertebral body which was detected by both readers. (c) Rib unfolded image showing mixed lesions in the right first rib (short arrows) and eighth thoracic vertebral body. (d) Fluorine-18 fludeoxyglucose (FDG) positron emission tomography/CT showing FDG uptake in the corresponding area of the first rib.

Figure 4. A 46-year-old female patient with left mastectomy due to breast cancer: (a) a sclerotic lesion in T10 vertebral body was detected on chest CT. (b) Another sclerotic lesion in right transverse process of T9 was missed on original coronal CT reading (arrow). (c) Readers detected two metastatic lesions (arrows in T9) on the Bone Reading image of the spine showing T-spines as one view with numbering. (d) Bone scan revealing hot uptake at the same site, T10 vertebral body (thin arrow) and the right transverse process of T9 (thick arrow).

portion of the upper ribs per slice of axial or coronal CT images is smaller owing to their acute curvature. After using Bone Reading CT software, the sensitivity and accuracy of lesion detection per-patient basis analysis by the radiology resident were increased (sensitivity, from 57.7% to 80.8%; accuracy, from 86.5% to 91.3%) compared with those of the experienced radiologist (84.6% and 92.1%, respectively).

In our study, the percentage of metastatic lesions with sclerotic character was higher than that in other studies.¹⁸ Quattrocchi et al¹⁹ have reported a changing pattern of bone metastasis in patients with breast cancer. They showed an increasing prevalence of sclerotic bone metastasis (32.1% vs 53.3%) between the

period 1996–2000 and the period 2001–2005. Recently, it has been known that bisphosphonate treatment and certain systemic anticancer treatment can influence CT appearance of bone metastasis in breast cancers.^{20–22} Bisphosphonate use owing to osteoporosis or systemic anticancer treatment before image diagnosis of bone metastasis might have influenced CT characteristics of bone lesions in our study population.

Bone is the preferential site of distant metastasis in breast cancer. The prevalence is known to be variable according to the stage and imaging technique used, ranging from 1.2% to up to 70%.^{22,23} In this study, the prevalence of bone metastasis was 20.6%. Approximately half of the patients (14/26) had a single

Table 4. Average reading time by reader and method

Reader	Chest CT	Bone Reading	p-value
R1	154.9 ± 43.3	57.2 ± 23.5	<0.001
R2	183.9 ± 43.3	84.7 ± 23.1	<0.001

R1, a board-certified chest radiologist with over 15 years' experience; R2, a second-year radiology resident.

Data are presented as average reading time in seconds ± the standard deviation for each reader and method.

Significant differences were considered at p -value <0.05.

lesion. Under a well-developed screening system, relatively early detection of breast cancer can result in a much lower prevalence of distant metastasis.²⁴ Readers might have difficulty in searching all thoracic bones through numerous CT slices to detect small metastatic lesions in low prevalence. However, bone metastases can eventually cause severe and debilitating effects and seriously impair quality of life without timely treatment. Therefore, using Bone Reading software in breast cancer can be very helpful for improving radiologist performance particularly in the detection of small and sclerotic bone lesions.

This study had several limitations. First, histopathologic correlation could not be obtained. Final diagnosis of lesions was achieved by means of closed clinical follow-up with confirmation by ¹⁸F-FDG-PET/CT and/or bone scintigraphy. However, FDG-PET/CT alone or combined with bone scintigraphy is commonly used as a gold standard in the diagnosis of bone metastasis.^{17,25} Second, as a retrospective study, imaging

modalities including chest CT, ¹⁸F-FDG-PET/CT and bone scintigraphy were not performed at the same time. Time interval of each modality might have weakened its validity to some degree. Third, patients who were diagnosed with bone metastasis during follow-up were included in the study group. Thus, hormonal or drug therapy before imaging detection of bone metastasis could change the CT patterns of bone metastasis and influence the diagnostic performance. Nevertheless, this is a general form of clinical practice. We believe our study reflects a reality of chest CT evaluation in breast cancer. Fourth, measurement of reading time did not include the loading or post-processing time of the Bone Reading program. Those processes are automatically performed by assigning specific data sets to the post-processing routine after completing CT scanning. Thus, such time was not measurable or noticeable by the radiologist. Last, we used two different CT scanners. However, because we used similar CT protocols with the same reconstruction slice thickness and kernel, the performance of lesion detection in original chest CT or Bone Reading application might not have been affected by different CT scanners.

In conclusion, our study showed that the use of advanced Bone Reading CT software could improve the reading performance of radiologists for the detection of thoracic bone metastases in patients with breast cancer with shortened reading time, especially for the inexperienced radiologist. By using Bone Reading CT software, readers could find small and sclerotic lesions that might be easily missed by original CT reading, rendering early diagnosis and timely treatment for patients with breast cancer.

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