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Correlation between mammographic findings and corresponding histopathology: Potential predictors for biological characteristics of breast diseases

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The present study retrospectively evaluated the mammographic findings of 606 Japanese women with breast cancer (median age 50 years; range 27–89 years) and correlated them with histopathological characteristics. Mammographic findings were evaluated with an emphasis on mass shape, margin, density, calcification, and the presence of architectural distortion; these findings were correlated with histopathological characteristics such as intrinsic subtype, histological grade, lymphovascular invasion, and the Ki-67 labeling index. An irregular mass shape and masses with a spiculated margin were significantly higher in the group of patients with luminal A breast cancer than in patients with masses that were lobular or round, or in tumors with an indistinct or microlobulated periphery ($P = 0.017$, $P = 0.024$, $P < 0.001$, and $P = 0.001$, respectively). Irregular mass shape and spiculated periphery were significantly lower in patients with Grade 3 cancer ($P < 0.001$ for both). In terms of lymphovascular invasion, there were significant differences between oval and irregular or round mass shape ($P = 0.008$ and $P = 0.034$), between tumors with a microlobulated and indistinct periphery ($P = 0.014$), between tumors with a punctate and amorphous or pleomorphic calcification shape ($P = 0.030$ and 0.038), and between the presence and absence of architectural distortion ($P = 0.027$). Equivalent or low-density masses were also higher in Grade 1 breast cancers ($P = 0.007$). There were significant differences in the Ki-67 labeling index between irregular and lobular or round tumors ($P < 0.001$ and $P = 0.014$), as well as between spiculated and indistinct or microlobulated tumors ($P < 0.001$ for both). Significant differences were noted in the mammographic features of different primary breast cancer subtypes. These proposed mammographic diagnostic criteria based on biological characteristics may contribute to a more accurate prediction of biological behavior of breast malignancies. (*Cancer Sci* 2011; 102: 2179–2185)

The incidence of breast cancer has increased worldwide, which is considered due, in part, to mass screening programs resulting in the discovery of clinically occult breast lesions. Mammographic screening has been demonstrated to reduce breast cancer mortality in both Western and Oriental populations.[1] This mortality may be as great as 63% in women attending for screening.[2] Therefore, million of mammographic examinations are being performed yearly worldwide, and mammography has become the gold standard for detecting breast disorders. Strict attention to high-quality interpretation is required for successful of a mammographic diagnosis. Thus, it is important to establish an accurate diagnostic system for mammography.

Traditionally, prognostic determinations are made mainly on the basis of pathological information, including histological grade and lymphovascular invasion.[3–5] In addition to histological information, the status of molecular markers that have prognostic and predictive value can contribute to the selection of an optimal treatment strategy. These markers include estrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor receptor 2 (HER2) and determining the status of these markers has become standard practice in the management of breast cancer because ER and HER2 positivity can predict a patient's response to endocrine therapy or targeted therapy with monoclonal antibodies directed against HER2.[6] In addition, the St Gallen international expert consensus meeting on the primary treatment of early breast cancer reported that features indicative of increased risk of recurrence, thus indirectly supporting the addition of chemotherapy to endocrine therapy, include lower expression of steroid hormone receptors, Grade 3 tumors, high proliferation (as measured by conventional or multigene assays), and extensive peritumoral vascular invasion.[7] However, these therapeutic determinations have been derived mainly from pathological information.

The appearance of tumors on mammograms has a generally good correlation with subsequent histological characteristics. For example, microcalcification is the hallmark of ductal carcinoma *in situ*;[8] spiculation is significantly correlated with low histologic grade; and ill-defined masses and microcalcifications are features of high-grade tumors.[8] Accurate correlation of mammographic findings with corresponding histopathologic features is considered one of the most important aspects of mammographic evaluation. Full histopathological information, including histological grades and intrinsic subtypes, is determined correctly after surgery.[9] Therefore, the purpose of the present study was to retrospectively evaluate mammographic findings and to compare the histopathological characteristics of the different tumors (i.e. intrinsic subtype, histological grade, lymphovascular invasion, and Ki-67 labeling index) in Japanese patients.

Materials and Methods

Patients. The mammographic and histopathologic features of 606 Japanese breast cancer patients who had undergone surgery at Tohoku University Hospital, Sendai, between January 2005 and June 2010 were reviewed retrospectively. All patients provided informed consent and the study protocol was approved by the Ethics Committee at Tohoku University Graduate School of Medicine. The median age of the patients was 50 years (range 27–89 years).

Imaging devices and breast tissue specimens. All mammographic examinations were performed with dedicated machines.

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Analog mammographic examinations were performed with one unit (MAMMOMAT 3000 Nova; Siemens, Erlangen, Germany) using a screen–film technique (Min-R 2000 Min-R EV; Kodak Health Imaging, Rochester, NY, USA). Digital mammograms were acquired by using a system with an amorphous selenium DirectRay digital detector (LOARD Selenia; Hologic, Waltham, MA, USA). The system was connected to a viewing monitor (MammoRead; TOYO, Tokyo, Japan).

Samples were stained using H&E. Histochemical and immunohistochemical analyses for ER, HER2, and Ki-67 were performed at the Department of Pathology, Tohoku University Hospital. Surgical specimens were fixed in 10% formaldehyde solution and cut into serial 5-mm slices, embedded in paraffin, cut into 4-μm sections, and placed on the glue-coated glass slides. We used the avidin–streptavidin immunoperoxidase method using the clone 6F11 antibody (Ventana, Tucson, AZ, USA) in an automated immunostainer (Benchmark System; Ventana). A standardized immunohistochemistry kit (Hercep-Test for Immunoenzymatic Staining; Dako, Copenhagen, Denmark) was used for HER2 staining. The Ki-67 labeling index was determined using an MIB-1 monoclonal antibody (code M7240; Dako). Both H&E and immunohistochemical staining were performed by a single experienced technician. Positive controls for ER and HER2 were breast carcinoma, whereas negative controls for immunostaining were hepatocellular carcinoma.

Imaging and histopathological analyses. Two experienced breast surgeons independently evaluated the mammographic findings. These two investigators were blinded as to the histopathological diagnosis and the clinical outcome of the patients. If there were discrepancies in the interpretation of the mammograms, a final decision was reached using consensus evaluations from eight experienced breast surgeons and radiologists. Mammographic findings were subsequently analyzed according to the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS).[10] The presence of a mass, calcifications, focal asymmetric density (FAD), and architectural distortion were each recorded. Figure 1 shows representative mammographic findings. Mass shape was tentatively classified into round, oval, lobular, and irregular. Margins were classified as microlobulated, indistinct, spiculated, and "other". Density was classified into high, equivalent, or low. Calcification shape was tentatively classified into punctate, amorphous, pleomorphic, and linear. Finally, FAD was classified as with or without architectural distortion.

Two experienced pathologists independently evaluated surgical specimens. Histopathological evaluations were based on the World Health Organization (WHO) histological classification of tumors of breast and Rosen's Breast Pathology.[11,12] The presence of ER was determined by nuclear staining and was graded from 0 to 8 using the Allred score, with positivity defined as a score of ≥3.[13] With regard to HER2 evaluation, membranous staining was graded as 0–1+, 2+, and 3+.[14] Samples scored as 2+ were subjected to FISH to calculate the gene copy ratio of *HER2* to *CEP17* (PathVysion HER2 DNA Probe kit; Abbott, Chicago, IL, USA). Positivity was defined as a *HER2*:*CEP17*

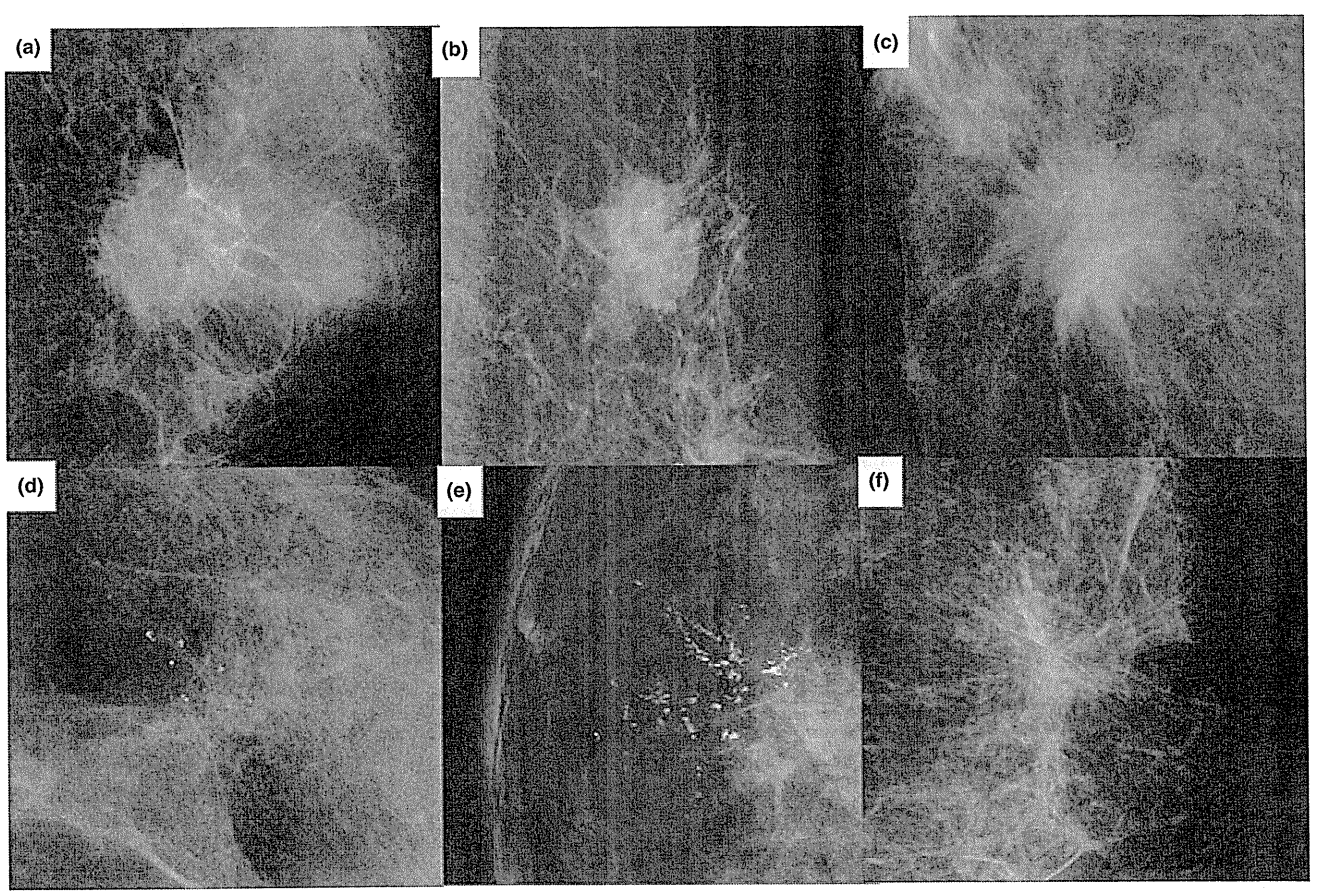

Fig. 1. Representative mammographic findings in breast carcinoma cases. (a) Round mass shape, microlobulated margin and intermediate density mass. (b) Lobular mass shape, indistinct margin, and high density mass. (c) Irregular mass shape, spiculated margin, and high-density mass. (d) Amorphous calcifications. (e) Pleomorphic or linear calcifications. (f) The presence of architectural distortion.

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signal ratio (FISH score) >2.2.[14] Histological grades were assessed according to the criteria of Elston and Ellis.[4] The Ki-67 immunoreactivity was evaluated by examining high-power fields and counting 1000 tumor cells in the hot spots.[15] In addition, the presence or absence of lymphovascular invasion was determined according to *Rosen's Breast Pathology*.[12] Intrinsic subtypes were classified according to the St Gallen international expert consensus on the primary therapy of early breast cancer 2011[16] as follows: luminal A was ER and/or PgR positive, HER2 negative, and Ki-67 low (<14%); luminal B was either ER and/or PgR positive, HER2 negative and Ki-67 high, or ER and/or PgR positive, any Ki-67, and HER2 overexpressed or amplified; the HER type was HER2 overexpressed or amplified and ER and PgR absent; and triple negative was ER, PgR and HER2 negative.

We compared mammographic findings, including mass shape, margin, density, calcification, FAD, and architectural distortion, with the histopathological characteristics of the tumors, including intrinsic subtype, histological grade, lymphovascular invasion, and the Ki-67 labeling index.

Statistical analysis. To compare mammographic findings with histopathological findings, multivariate analysis was used. All analyses were performed using SPSS version 10.0 (SPSS Inc., Chicago, IL, USA), with $P < 0.05$ taken to indicate significant differences.

Results

Comparison of mammographic findings with intrinsic subtype. Figure 2 summarizes the results of the numbers and ratios of each mammographic finding according to intrinsic subtype. In the luminal A group, significant differences were identified between masses that were irregular and lobular or round ($P = 0.017$ and $P = 0.024$), between those that had speculated and indistinct or microlobulated margins ($P < 0.001$ and $P = 0.001$), between those showing amorphous and pleomorphic calcification ($P = 0.044$), and between the presence and absence of architectural distortion ($P = 0.002$). In the HER group, significant differences were identified between masses that were irregular and oval or round ($P = 0.009$ and $P < 0.001$), between masses that were lobular and round ($P = 0.021$), and between those that had spiculated and microlobulated margins ($P = 0.005$). In the triple negative group, significant differences were identified between masses that had spiculated and

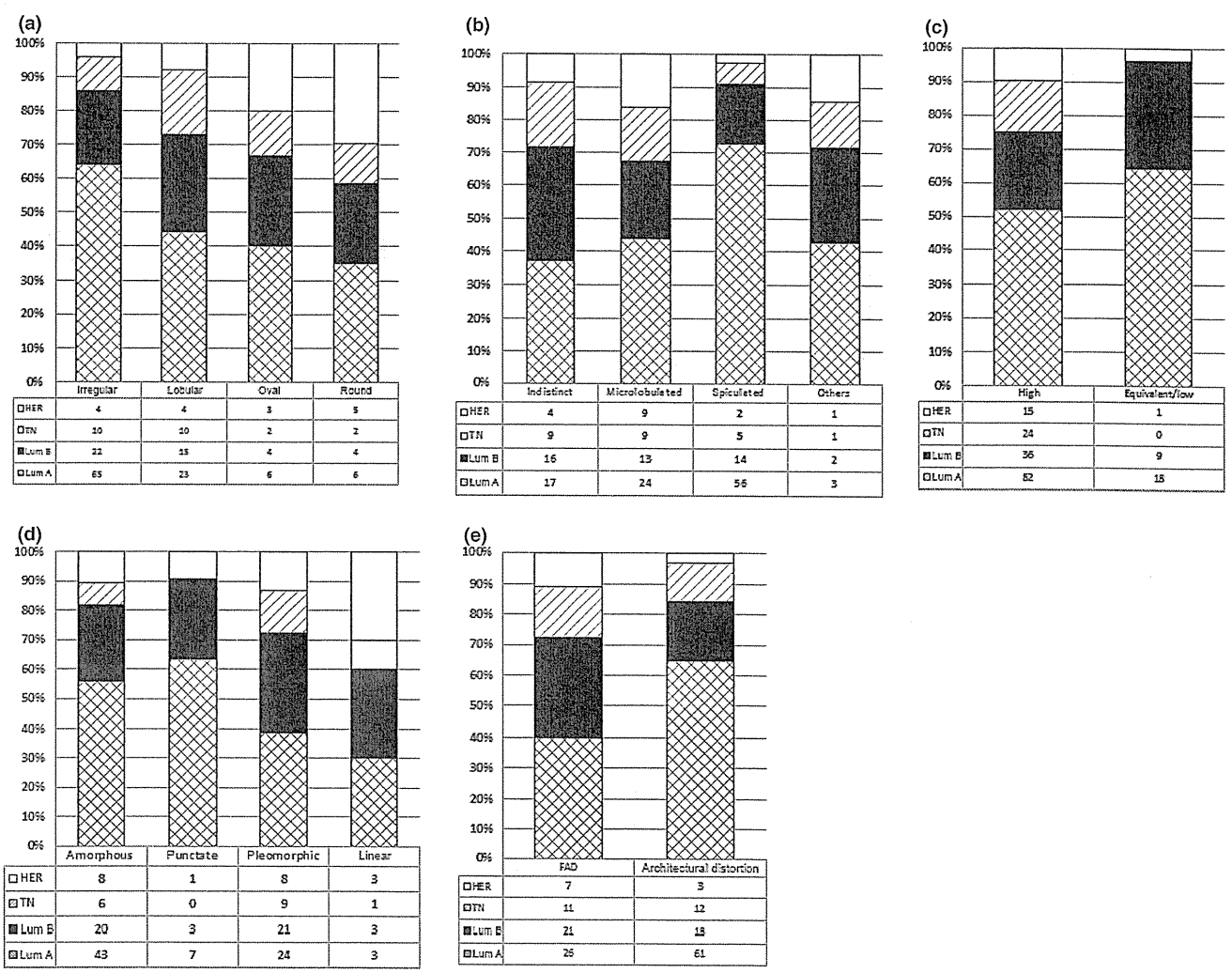

Fig. 2. Correlation between mammographic findings and intrinsic subtype: (a) mass shape, (b) margin, (c) density, (d) calcification shape, and (e) focal asymmetric density (FAD) and architectural distortion. HER, human epidermal growth factor receptor; TN, triple negative; Lum A, luminal A; Lum B, luminal B.

indistinct margins ($P = 0.027$), as well as between those identified as having high and equivalent or low density ($P = 0.027$).

Comparison of mammographic findings with histological grade. Figure 3 summarizes the results of the numbers and ratios of each mammographic finding according to histological grade. There were significant differences between irregular and lobular or oval mass shape in Grade 3 ($P < 0.001$ for all). Furthermore, in Grade 1 tumors, significant differences were found between with an indistinct and microlobulated or spiculated periphery ($P = 0.030$ and $P = 0.003$), between those with spiculated and indistinct or microlobulated margins ($P < 0.001$, respectively), between those identified as high and equivalent or low density ($P = 0.047$), and between those with a linear and amorphous calcification shape ($P = 0.027$).

Comparison of mammographic findings with lymphovascular invasion. Figure 4 summarizes the results for the numbers and ratios of each mammographic finding according to lymphovascular invasion. There were significant differences between oval and irregular or round mass shape ($P = 0.008$ and $P = 0.034$), between microlobulated and indistinct periphery ($P = 0.014$), between punctate and amorphous or pleomorphic calcification shape ($P = 0.030$ and 0.038), and between presence and absence of architectural distortion ($P = 0.027$).

Comparison of mammographic findings with the Ki-67 labeling index. Figure 5 summarizes the results of correlations between mammographic findings and the Ki-67 labeling index. The Ki-67 labeling index according to mass shape was 15.74 ± 6.21 for irregular masses, 38.82 ± 13.10 for lobular masses, 36.22 ± 15.75 for oval masses, and 37.85 ± 14.95 for round masses. According to mass periphery, the Ki-67 labeling index was 35.80 ± 28.51, 34.56 ± 29.76, 11.73 ± 10.86, and 27.50 ± 24.75 for tumors with indistinct, microlobulated, spiculated, and "other" margins, respectively. For tumors with a high and equivalent or low mass density, Ki-67 labeling index was 27.68 ± 26.75 and 13.14 ± 14.10, respectively. Tumors that showed amorphous, punctate, pleomorphic, and linear calcification had a Ki-67 labeling index of 24.55 ± 7.58, 26.00 ± 18.27, 24.68 ± 9.43, and 16.00 ± 17.23, respectively. In tumors without and with architectural distortion, the Ki-67 labeling index was 22.27 ± 8.64 and 25.02 ± 7.43, respectively. There were significant differences between irregular and lobular or round ($P < 0.001$ and $P = 0.014$), spiculated and indistinct or microlobulated ($P < 0.001$ for all), and high and equivalent or low density ($P = 0.018$) groups. A trend for a positive correlation was detected between irregular and oval mass shape, but the difference did not reach statistical significance ($P = 0.062$).

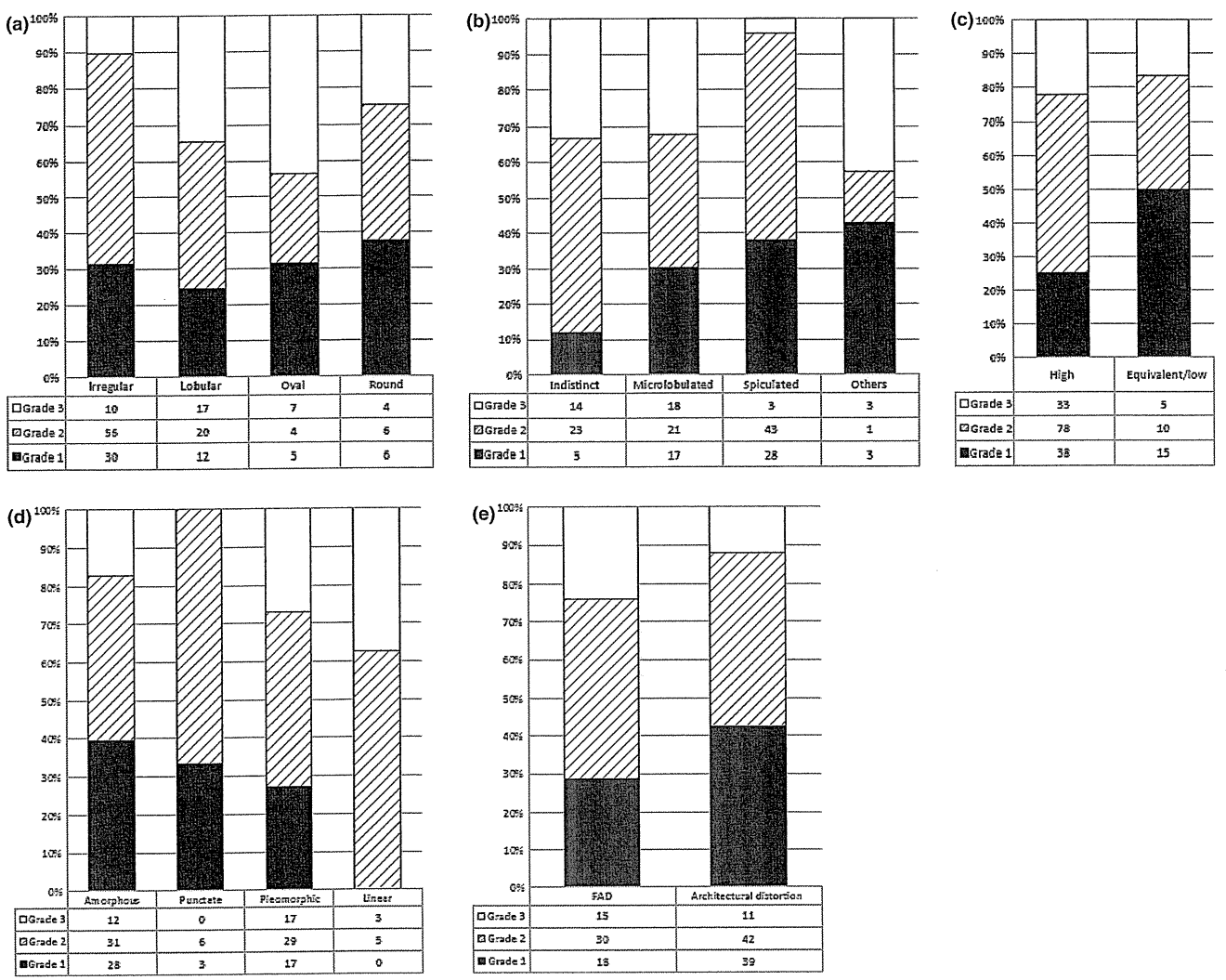

Fig. 3. Correlation between mammographic findings and histological grade: (a) mass shape, (b) margin, (c) density, (d) calcification shape, and (e) focal asymmetric density (FAD) and architectural distortion.

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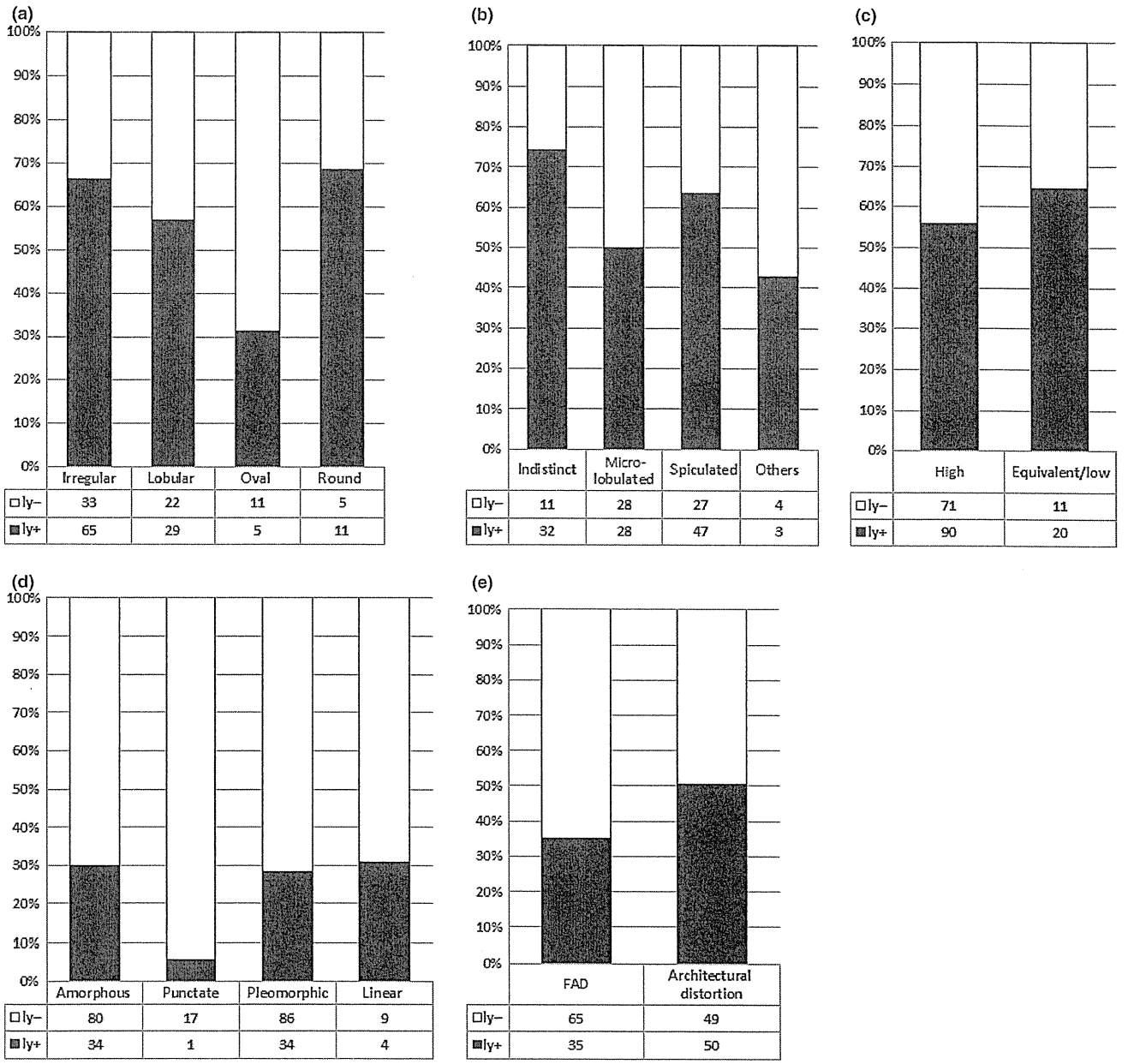

Fig. 4. Correlation between mammographic findings and lymphovascular invasion: (a) mass shape, (b) margin, (c) density, (d) calcification shape, and (e) focal asymmetric density (FAD) and architectural distortion. ly–, no lymphovascular invasion; ly+, lymphovascular invasion.

There were no significant differences according to calcification shape and the presence of architectural distortion.

Discussion

Histological grade is well known to have a strong correlation with clinical outcome in patients with breast cancer.[4] Accumulating clinical evidence suggests that prognostic factors influencing breast cancer extend beyond the traditional tumor histological grade.[17] Several factors, including ER expression, HER2 status, and lymphovascular invasion, have been clearly demonstrated in recent years to contribute significantly to the management and subsequent prognosis of patients with breast cancer.[7,18] Therefore, an accurate correlation between mammographic findings and their corresponding histopathological features is considered most important in mammographic evaluation. Mammographic findings may provide insights into pathological and biological features, including tumor cell characteristics, histological grade, and cell proliferation. We attempted to determine which finding is more relevant with regard to the newly defined subtype of breast carcinoma cells. Therefore, the purpose of the present study was to evaluate the correlation between mammographic findings (e.g. mass shape, margin, density, calcification shape, FAD, and the presence of architectural distortion) with intrinsic subtype, histological grade, lymphovascular invasion, and the Ki-67 labeling index in breast cancer patients.

Several previous studies evaluated the correlation between mammographic findings and histopathological characteristics in individual patients.[8,19–21] A number of independent groups demonstrated that masses with a spiculated periphery were associated with a good outcome in patients.[19,20] Conversely,

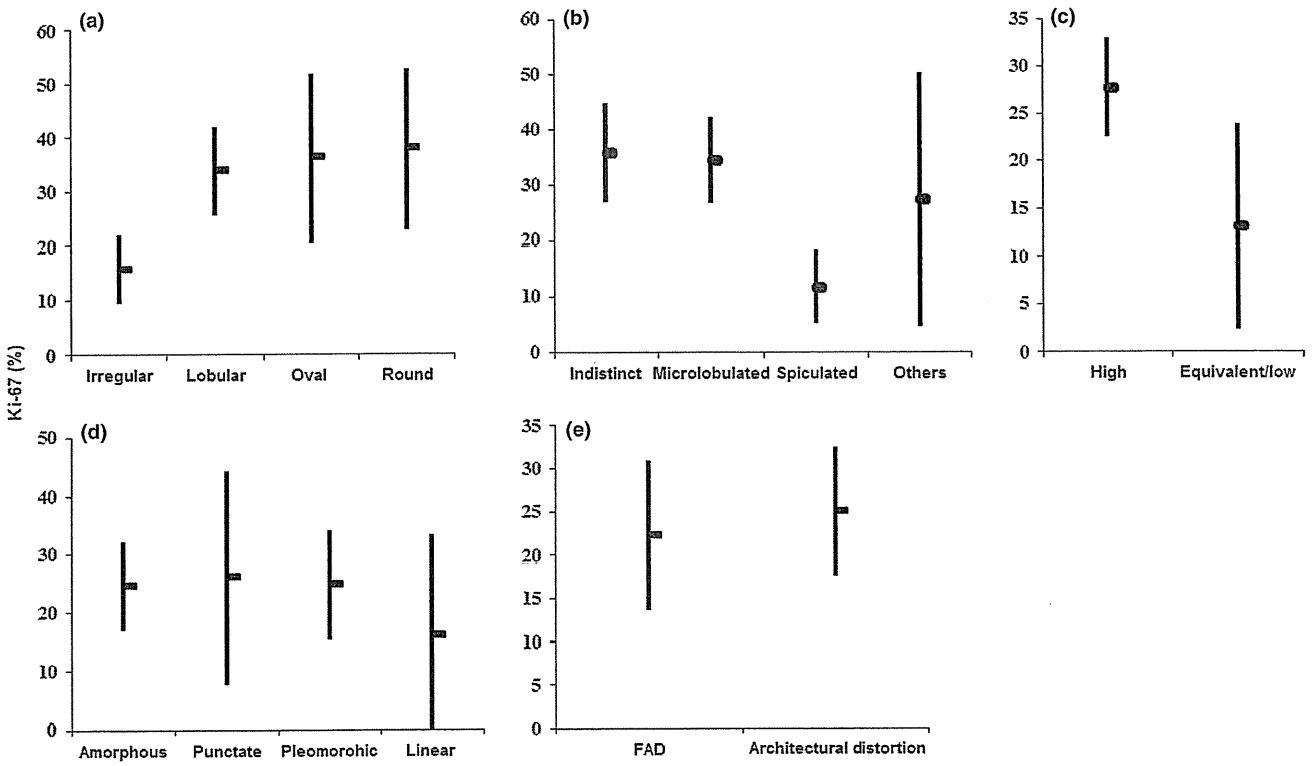

Fig. 5. Correlation between mammographic findings and Ki-67 labeling index: (a) mass shape, (b) margin, (c) density, (d) calcification shape, and (e) focal asymmetric density (FAD) and architectural distortion.

well-defined masses were associated with triple-negative breast cancer.[8,21] The results of the present study demonstrate that is a higher incidence of lower histological grade in masses with an irregular shape and/or spiculated margins, although a higher histological grade is not necessarily associated with irregular mass shape or spiculated margins. In addition, correlation of mammographic findings with the intrinsic subtype demonstrated that irregular mass shape and/or spiculated margin masses were significantly more frequently detected in luminal A breast cancers than in the other subtypes in this cohort of Japanese patients. However, oval and round mass shape and/or indistinct and microlobulated margin masses were significantly more frequently detected in triple-negative breast cancers or HER breast cancers. As for architectural distortion, the ratio of architectural distortion was significantly higher in luminal A cases and also tended to be associated with histological Grade 1. Together, these results suggest that poorly differentiated breast carcinoma cells are associated with good histological grade and luminal A subclassification. However, well-differentiated carcinoma cells are associated with adverse clinical grading and negative ER status.

Previous studies have demonstrated that these differentiations were related somewhat with adhesion factors.[22,23] Loss of adhesion factors in carcinoma cell is considered to play a role in the characteristic histological appearance of invasive carcinoma as loosely dispersed linear columns of cells and a typical discrete mass.[22] This more diffuse infiltrative pattern may explain some of the typical imaging appearances of tumors, such as spiculation and distortion.[22] In addition, adhesion factors are correlated with high histologic grade.[23] Therefore, adhesion factors may be considered to be correlated with the results of the present study in that spiculated breast cancers have a good clinical outcome and histological Grade 1. However, it is also true that numerous biological mechanisms underlying the association between the process of infiltration and histopathological characteristics remain unknown and that further investigations are required to confirm interpretation of mammography in terms of the biological and histopathologic characteristics of tumors.

To the best of our knowledge, this is the first study to compare mammographic findings with the Ki-67 labeling index and histopathological lymphovascular invasion. The results of the present study demonstrated that there was a higher incidence of a lower Ki-67 labeling index in tumors with an irregular mass shape, spiculated periphery, and equivalent or low mass density. Irregular mass shape and a spiculated periphery are well-known predictors of malignancy, but the results of the present study seem to suggest that findings of irregular shape and a spiculated periphery are relatively good prognostic predictors in terms of the Ki-67 labeling index. In addition, the results of the present study demonstrate that lymphovascular invasion was significantly greater in cases in which there was architectural distortion; however, the incidence of lymphovascular invasion was not significantly higher in spiculated masses. These results all suggest that the correlation between findings of radiological dist ortion and the mechanisms of lymphovascular invasion remain unknown and further investigations are required.

We also examined the correlation between mammographic calcification shape and histopathological characteristics. Previous studies have reported that triple-negative breast cancers are more likely to exhibit comedo calcifications.[8] In addition, the high frequency of comedo calcification in triple-negative breast cancers may represent a consequence of high histologic grade.[8] The presence of mammographic comedo calcification has also been reported to be associated with a poor prognosis in small screening-detected invasive cancers.[19] The results of the present study also demonstrate that non-necrotic calcifications, including amorphous and punctate calcification, are associated with a higher ratio of luminal A cases, whereas necrotic calcifications, including pleomorphic and linear calcification, were

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associated with a higher ratio of HER breast cancers. In addition, necrotic calcifications tended to be associated with a higher histological grade than non-necrotic calcifications. Therefore, the results suggest that the type of calcification may become a prognostic factor for breast malignancies.

We noted significant differences in the mammographic features of different primary breast cancer immunophenotypes in the present study. Stratifying the mammographic features according to immunophenotypes reveals distinct differences among cancer subtypes. However, the limitations of the present study include that fact that the study was retrospective in nature and was performed in a single institute, namely Tohoku University Hospital. Therefore, further investigations are needed, including analysis in several different institutions to further refine the new mammographic criteria. Biological and histopathological differences may result in imaging differences that may help us better understand the development of breast cancer. These proposed mammographic diagnostic criteria based on biological characteristics may contribute to a more accurate prediction of the biological behavior of breast malignancies.

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Disclosure Statement

The authors have no conflict of interest.

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Correlation between mammographic findings and corresponding histopathology: Potential predictors for biological characteristics of breast diseases

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The present study retrospectively evaluated the mammographic findings of 606 Japanese women with breast cancer (median age 50 years; range 27–89 years) and correlated them with histopathological characteristics. Mammographic findings were evaluated with an emphasis on mass shape, margin, density, calcification, and the presence of architectural distortion; these findings were correlated with histopathological characteristics such as intrinsic subtype, histological grade, lymphovascular invasion, and the Ki-67 labeling index. An irregular mass shape and masses with a spiculated margin were significantly higher in the group of patients with luminal A breast cancer than in patients with masses that were lobular or round, or in tumors with an indistinct or microlobulated periphery ($P = 0.017$, $P = 0.024$, $P < 0.001$, and $P = 0.001$, respectively). Irregular mass shape and spiculated periphery were significantly lower in patients with Grade 3 cancer ($P < 0.001$ for both). In terms of lymphovascular invasion, there were significant differences between oval and irregular or round mass shape ($P = 0.008$ and $P = 0.034$), between tumors with a microlobulated and indistinct periphery ($P = 0.014$), between tumors with a punctate and amorphous or pleomorphic calcification shape ($P = 0.030$ and 0.038), and between the presence and absence of architectural distortion ($P = 0.027$). Equivalent or low-density masses were also higher in Grade 1 breast cancers ($P = 0.007$). There were significant differences in the Ki-67 labeling index between irregular and lobular or round tumors ($P < 0.001$ and $P = 0.014$), as well as between spiculated and indistinct or microlobulated tumors ($P < 0.001$ for both). Significant differences were noted in the mammographic features of different primary breast cancer subtypes. These proposed mammographic diagnostic criteria based on biological characteristics may contribute to a more accurate prediction of biological behavior of breast malignancies. (*Cancer Sci* 2011; 102: 2179–2185)

The incidence of breast cancer has increased worldwide, which is considered due, in part, to mass screening programs resulting in the discovery of clinically occult breast lesions. Mammographic screening has been demonstrated to reduce breast cancer mortality in both Western and Oriental populations.[1] This mortality may be as great as 63% in women attending for screening.[2] Therefore, million of mammographic examinations are being performed yearly worldwide, and mammography has become the gold standard for detecting breast disorders. Strict attention to high-quality interpretation is required for successful of a mammographic diagnosis. Thus, it is important to establish an accurate diagnostic system for mammography.

Traditionally, prognostic determinations are made mainly on the basis of pathological information, including histological grade and lymphovascular invasion.[3–5] In addition to histological information, the status of molecular markers that have prognostic and predictive value can contribute to the selection of an optimal treatment strategy. These markers include estrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor receptor 2 (HER2) and determining the status of these markers has become standard practice in the management of breast cancer because ER and HER2 positivity can predict a patient's response to endocrine therapy or targeted therapy with monoclonal antibodies directed against HER2.[6] In addition, the St Gallen international expert consensus meeting on the primary treatment of early breast cancer reported that features indicative of increased risk of recurrence, thus indirectly supporting the addition of chemotherapy to endocrine therapy, include lower expression of steroid hormone receptors, Grade 3 tumors, high proliferation (as measured by conventional or multigene assays), and extensive peritumoral vascular invasion.[7] However, these therapeutic determinations have been derived mainly from pathological information.

The appearance of tumors on mammograms has a generally good correlation with subsequent histological characteristics. For example, microcalcification is the hallmark of ductal carcinoma *in situ*;[8] spiculation is significantly correlated with low histologic grade; and ill-defined masses and microcalcifications are features of high-grade tumors.[8] Accurate correlation of mammographic findings with corresponding histopathologic features is considered one of the most important aspects of mammographic evaluation. Full histopathological information, including histological grades and intrinsic subtypes, is determined correctly after surgery.[9] Therefore, the purpose of the present study was to retrospectively evaluate mammographic findings and to compare the histopathological characteristics of the different tumors (i.e. intrinsic subtype, histological grade, lymphovascular invasion, and Ki-67 labeling index) in Japanese patients.

Materials and Methods

Patients. The mammographic and histopathologic features of 606 Japanese breast cancer patients who had undergone surgery at Tohoku University Hospital, Sendai, between January 2005 and June 2010 were reviewed retrospectively. All patients provided informed consent and the study protocol was approved by the Ethics Committee at Tohoku University Graduate School of Medicine. The median age of the patients was 50 years (range 27–89 years).

Imaging devices and breast tissue specimens. All mammographic examinations were performed with dedicated machines.

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Analog mammographic examinations were performed with one unit (MAMMOMAT 3000 Nova; Siemens, Erlangen, Germany) using a screen–film technique (Min-R 2000 Min-R EV; Kodak Health Imaging, Rochester, NY, USA). Digital mammograms were acquired by using a system with an amorphous selenium DirectRay digital detector (LOARD Selenia; Hologic, Waltham, MA, USA). The system was connected to a viewing monitor (MammoRead; TOYO, Tokyo, Japan).

Samples were stained using H&E. Histochemical and immunohistochemical analyses for ER, HER2, and Ki-67 were performed at the Department of Pathology, Tohoku University Hospital. Surgical specimens were fixed in 10% formaldehyde solution and cut into serial 5-mm slices, embedded in paraffin, cut into 4-μm sections, and placed on the glue-coated glass slides. We used the avidin–streptavidin immunoperoxidase method using the clone 6F11 antibody (Ventana, Tucson, AZ, USA) in an automated immunostainer (Benchmark System; Ventana). A standardized immunohistochemistry kit (Hercep-Test for Immunoenzymatic Staining; Dako, Copenhagen, Denmark) was used for HER2 staining. The Ki-67 labeling index was determined using an MIB-1 monoclonal antibody (code M7240; Dako). Both H&E and immunohistochemical staining were performed by a single experienced technician. Positive controls for ER and HER2 were breast carcinoma, whereas negative controls for immunostaining were hepatocellular carcinoma.

Imaging and histopathological analyses. Two experienced breast surgeons independently evaluated the mammographic findings. These two investigators were blinded as to the histopathological diagnosis and the clinical outcome of the patients. If there were discrepancies in the interpretation of the mammograms, a final decision was reached using consensus evaluations from eight experienced breast surgeons and radiologists. Mammographic findings were subsequently analyzed according to the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS).[10] The presence of a mass, calcifications, focal asymmetric density (FAD), and architectural distortion were each recorded. Figure 1 shows representative mammographic findings. Mass shape was tentatively classified into round, oval, lobular, and irregular. Margins were classified as microlobulated, indistinct, spiculated, and "other". Density was classified into high, equivalent, or low. Calcification shape was tentatively classified into punctate, amorphous, pleomorphic, and linear. Finally, FAD was classified as with or without architectural distortion.

Two experienced pathologists independently evaluated surgical specimens. Histopathological evaluations were based on the World Health Organization (WHO) histological classification of tumors of breast and Rosen's Breast Pathology.[11,12] The presence of ER was determined by nuclear staining and was graded from 0 to 8 using the Allred score, with positivity defined as a score of ≥3.[13] With regard to HER2 evaluation, membranous staining was graded as 0–1+, 2+, and 3+.[14] Samples scored as 2+ were subjected to FISH to calculate the gene copy ratio of *HER2* to *CEP17* (PathVysion HER2 DNA Probe kit; Abbott, Chicago, IL, USA). Positivity was defined as a *HER2*:*CEP17*

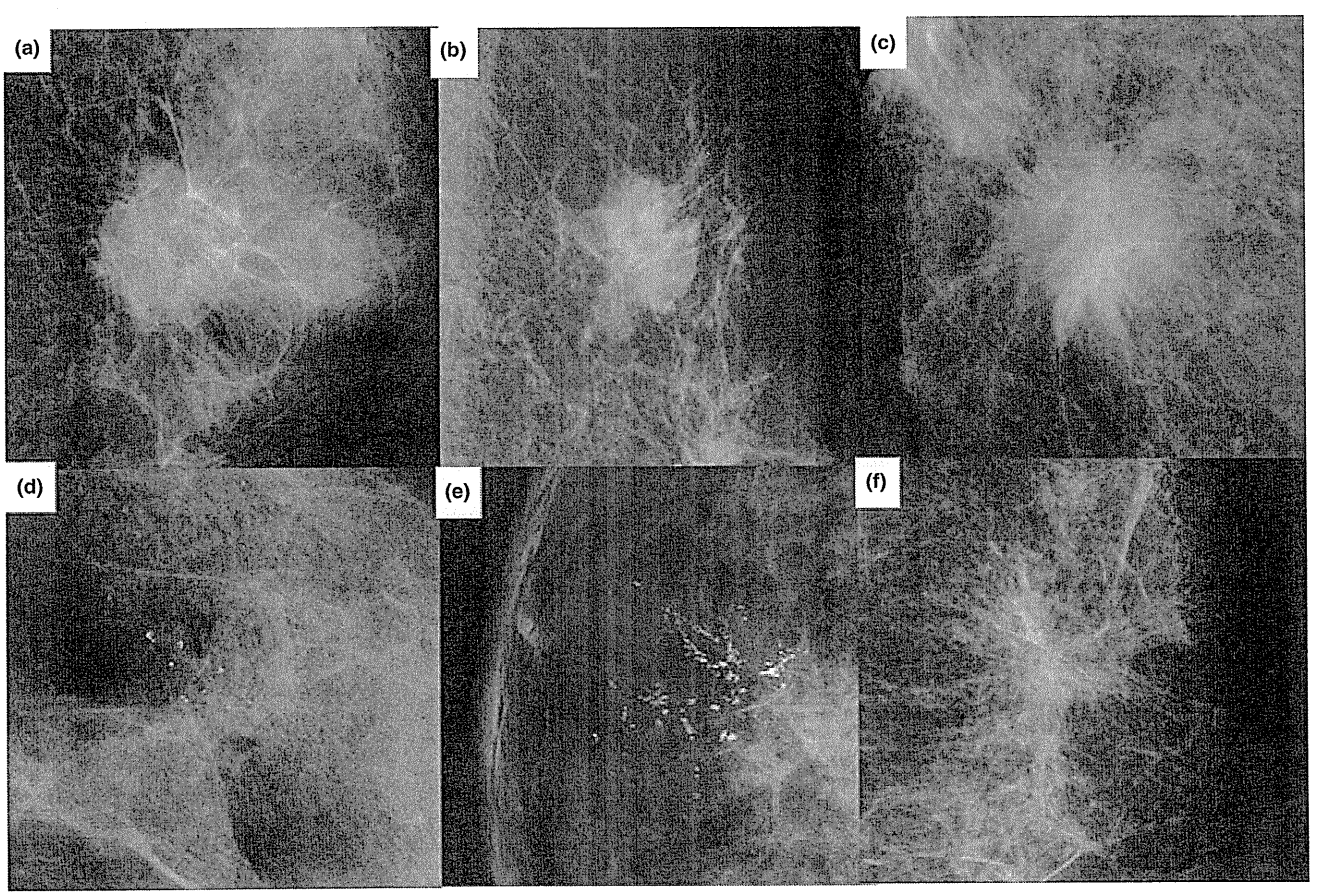

Fig. 1. Representative mammographic findings in breast carcinoma cases. (a) Round mass shape, microlobulated margin and intermediate density mass. (b) Lobular mass shape, indistinct margin, and high density mass. (c) Irregular mass shape, spiculated margin, and high-density mass. (d) Amorphous calcifications. (e) Pleomorphic or linear calcifications. (f) The presence of architectural distortion.

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signal ratio (FISH score) >2.2.[14] Histological grades were assessed according to the criteria of Elston and Ellis.[4] The Ki-67 immunoreactivity was evaluated by examining high-power fields and counting 1000 tumor cells in the hot spots.[15] In addition, the presence or absence of lymphovascular invasion was determined according to *Rosen's Breast Pathology*.[12] Intrinsic subtypes were classified according to the St Gallen international expert consensus on the primary therapy of early breast cancer 2011[16] as follows: luminal A was ER and/or PgR positive, HER2 negative, and Ki-67 low (<14%); luminal B was either ER and/or PgR positive, HER2 negative and Ki-67 high, or ER and/or PgR positive, any Ki-67, and HER2 overexpressed or amplified; the HER type was HER2 overexpressed or amplified and ER and PgR absent; and triple negative was ER, PgR and HER2 negative.

We compared mammographic findings, including mass shape, margin, density, calcification, FAD, and architectural distortion, with the histopathological characteristics of the tumors, including intrinsic subtype, histological grade, lymphovascular invasion, and the Ki-67 labeling index.

Statistical analysis. To compare mammographic findings with histopathological findings, multivariate analysis was used. All analyses were performed using SPSS version 10.0 (SPSS Inc., Chicago, IL, USA), with $P < 0.05$ taken to indicate significant differences.

Results

Comparison of mammographic findings with intrinsic subtype. Figure 2 summarizes the results of the numbers and ratios of each mammographic finding according to intrinsic subtype. In the luminal A group, significant differences were identified between masses that were irregular and lobular or round ($P = 0.017$ and $P = 0.024$), between those that had speculated and indistinct or microlobulated margins ($P < 0.001$ and $P = 0.001$), between those showing amorphous and pleomorphic calcification ($P = 0.044$), and between the presence and absence of architectural distortion ($P = 0.002$). In the HER group, significant differences were identified between masses that were irregular and oval or round ($P = 0.009$ and $P < 0.001$), between masses that were lobular and round ($P = 0.021$), and between those that had spiculated and microlobulated margins ($P = 0.005$). In the triple negative group, significant differences were identified between masses that had spiculated and

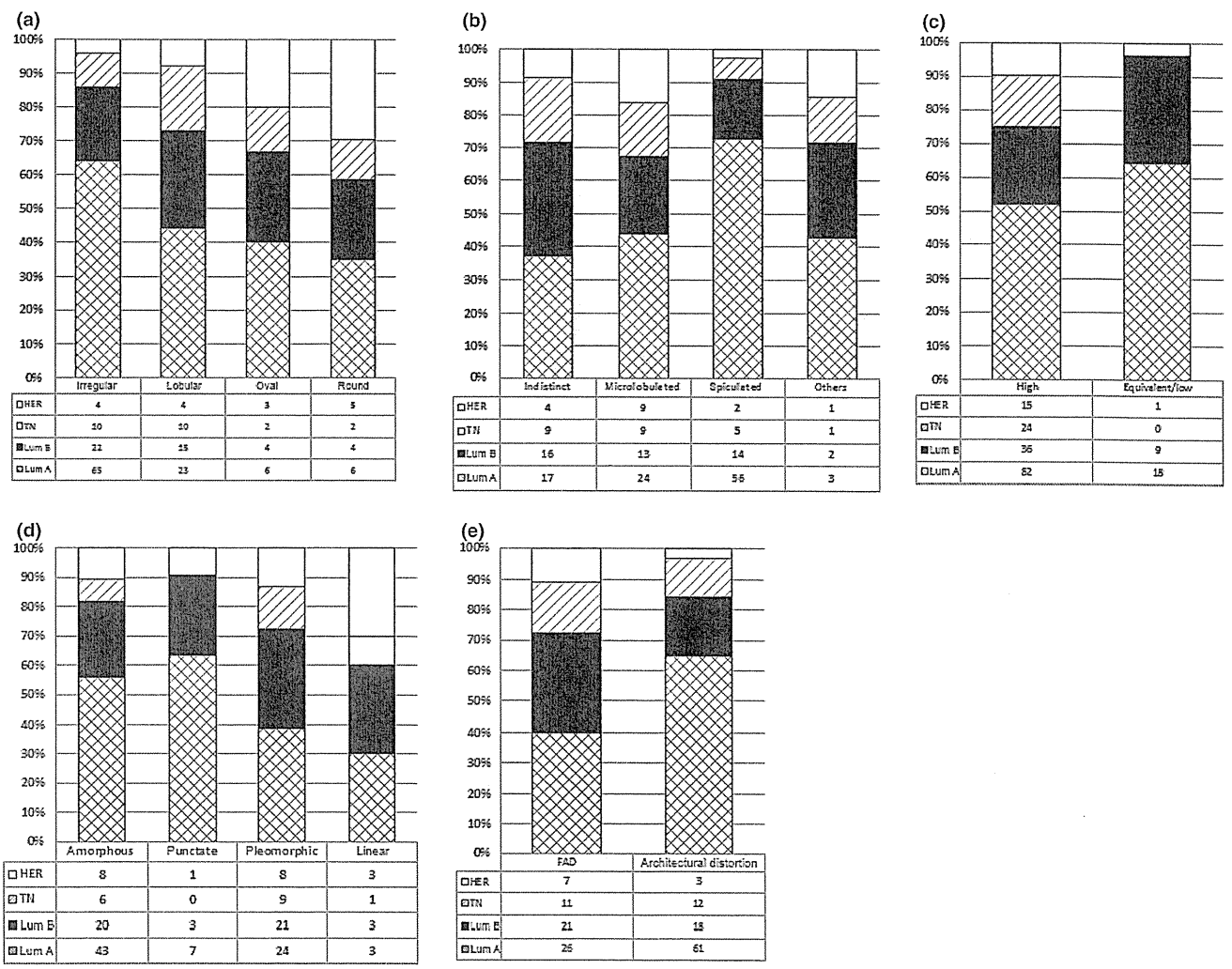

Fig. 2. Correlation between mammographic findings and intrinsic subtype: (a) mass shape, (b) margin, (c) density, (d) calcification shape, and (e) focal asymmetric density (FAD) and architectural distortion. HER, human epidermal growth factor receptor; TN, triple negative; Lum A, luminal A; Lum B, luminal B.

indistinct margins ($P = 0.027$), as well as between those identified as having high and equivalent or low density ($P = 0.027$).

Comparison of mammographic findings with histological grade. Figure 3 summarizes the results of the numbers and ratios of each mammographic finding according to histological grade. There were significant differences between irregular and lobular or oval mass shape in Grade 3 ($P < 0.001$ for all). Furthermore, in Grade 1 tumors, significant differences were found between with an indistinct and microlobulated or spiculated periphery ($P = 0.030$ and $P = 0.003$), between those with spiculated and indistinct or microlobulated margins ($P < 0.001$, respectively), between those identified as high and equivalent or low density ($P = 0.047$), and between those with a linear and amorphous calcification shape ($P = 0.027$).

Comparison of mammographic findings with lymphovascular invasion. Figure 4 summarizes the results for the numbers and ratios of each mammographic finding according to lymphovascular invasion. There were significant differences between oval and irregular or round mass shape ($P = 0.008$ and $P = 0.034$), between microlobulated and indistinct periphery ($P = 0.014$), between punctate and amorphous or pleomorphic calcification shape ($P = 0.030$ and 0.038), and between presence and absence of architectural distortion ($P = 0.027$).

Comparison of mammographic findings with the Ki-67 labeling index. Figure 5 summarizes the results of correlations between mammographic findings and the Ki-67 labeling index. The Ki-67 labeling index according to mass shape was 15.74 ± 6.21 for irregular masses, 38.82 ± 13.10 for lobular masses, 36.22 ± 15.75 for oval masses, and 37.85 ± 14.95 for round masses. According to mass periphery, the Ki-67 labeling index was 35.80 ± 28.51, 34.56 ± 29.76, 11.73 ± 10.86, and 27.50 ± 24.75 for tumors with indistinct, microlobulated, spiculated, and "other" margins, respectively. For tumors with a high and equivalent or low mass density, Ki-67 labeling index was 27.68 ± 26.75 and 13.14 ± 14.10, respectively. Tumors that showed amorphous, punctate, pleomorphic, and linear calcification had a Ki-67 labeling index of 24.55 ± 7.58, 26.00 ± 18.27, 24.68 ± 9.43, and 16.00 ± 17.23, respectively. In tumors without and with architectural distortion, the Ki-67 labeling index was 22.27 ± 8.64 and 25.02 ± 7.43, respectively. There were significant differences between irregular and lobular or round ($P < 0.001$ and $P = 0.014$), spiculated and indistinct or microlobulated ($P < 0.001$ for all), and high and equivalent or low density ($P = 0.018$) groups. A trend for a positive correlation was detected between irregular and oval mass shape, but the difference did not reach statistical significance ($P = 0.062$).

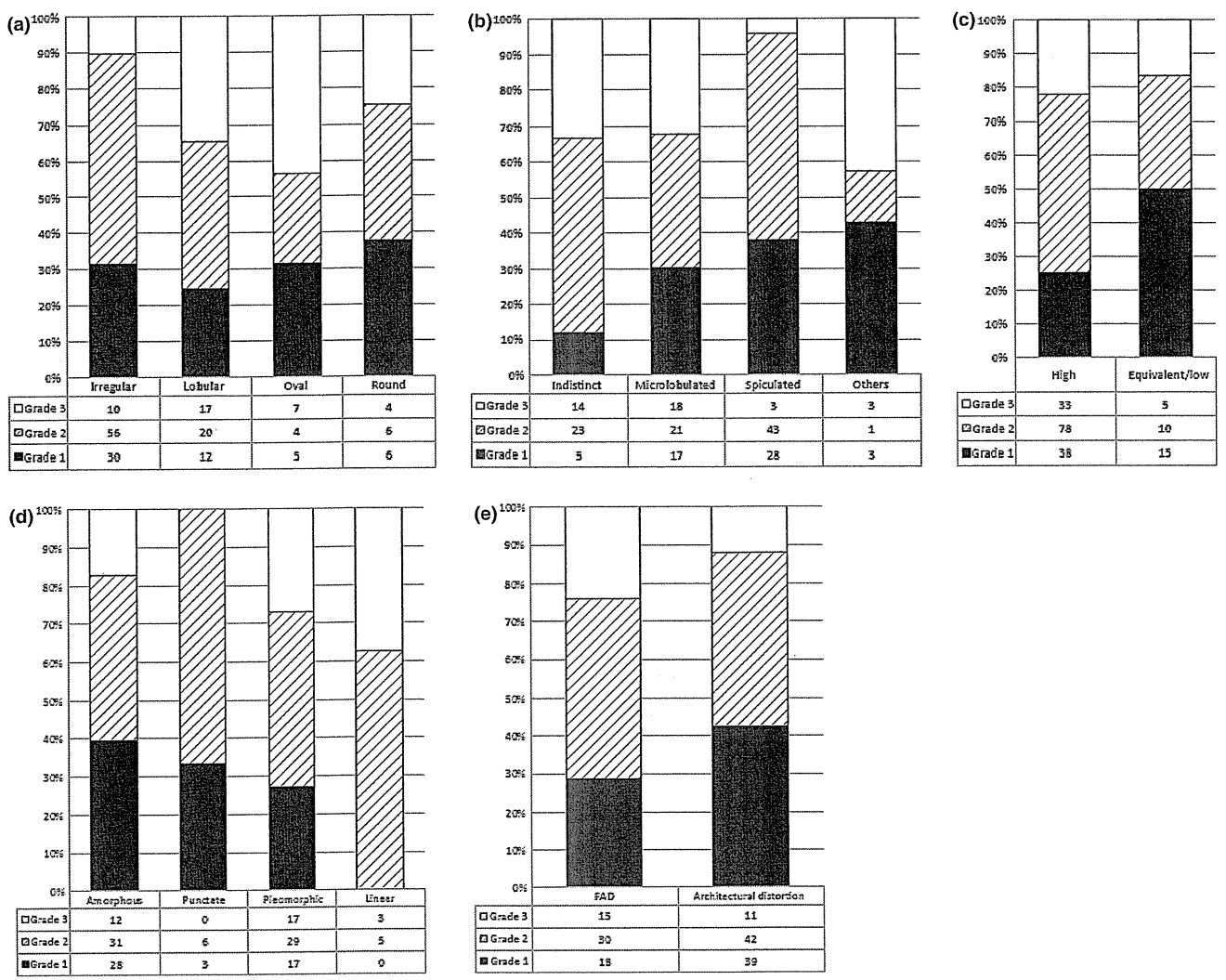

Fig. 3. Correlation between mammographic findings and histological grade: (a) mass shape, (b) margin, (c) density, (d) calcification shape, and (e) focal asymmetric density (FAD) and architectural distortion.

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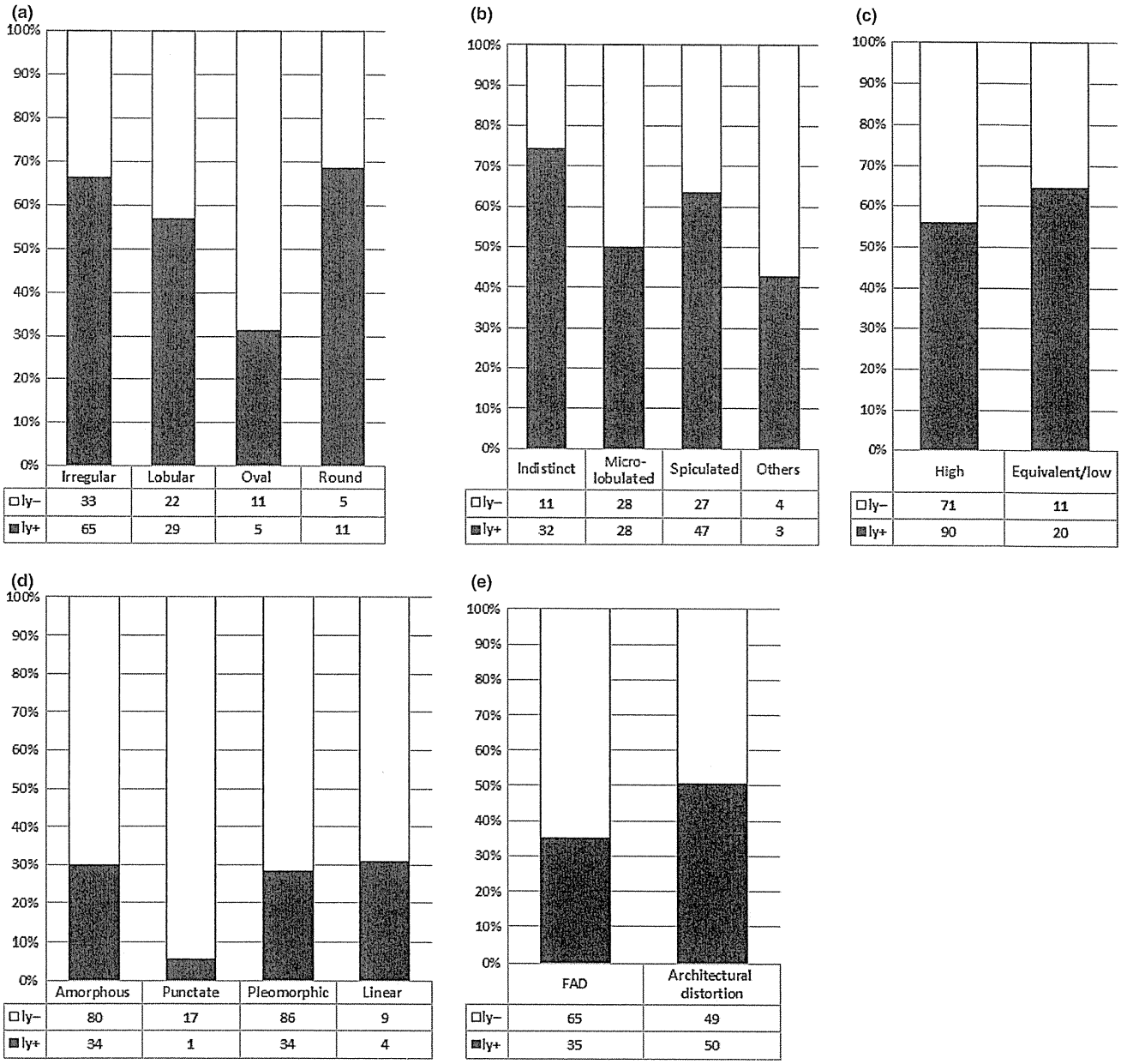

Fig. 4. Correlation between mammographic findings and lymphovascular invasion: (a) mass shape, (b) margin, (c) density, (d) calcification shape, and (e) focal asymmetric density (FAD) and architectural distortion. ly–, no lymphovascular invasion; ly+, lymphovascular invasion.

There were no significant differences according to calcification shape and the presence of architectural distortion.

Discussion

Histological grade is well known to have a strong correlation with clinical outcome in patients with breast cancer.[4] Accumulating clinical evidence suggests that prognostic factors influencing breast cancer extend beyond the traditional tumor histological grade.[17] Several factors, including ER expression, HER2 status, and lymphovascular invasion, have been clearly demonstrated in recent years to contribute significantly to the management and subsequent prognosis of patients with breast cancer.[7,18] Therefore, an accurate correlation between mammographic findings and their corresponding histopathological features is considered most important in mammographic evaluation. Mammographic findings may provide insights into pathological and biological features, including tumor cell characteristics, histological grade, and cell proliferation. We attempted to determine which finding is more relevant with regard to the newly defined subtype of breast carcinoma cells. Therefore, the purpose of the present study was to evaluate the correlation between mammographic findings (e.g. mass shape, margin, density, calcification shape, FAD, and the presence of architectural distortion) with intrinsic subtype, histological grade, lymphovascular invasion, and the Ki-67 labeling index in breast cancer patients.

Several previous studies evaluated the correlation between mammographic findings and histopathological characteristics in individual patients.[8,19–21] A number of independent groups demonstrated that masses with a spiculated periphery were associated with a good outcome in patients.[19,20] Conversely,

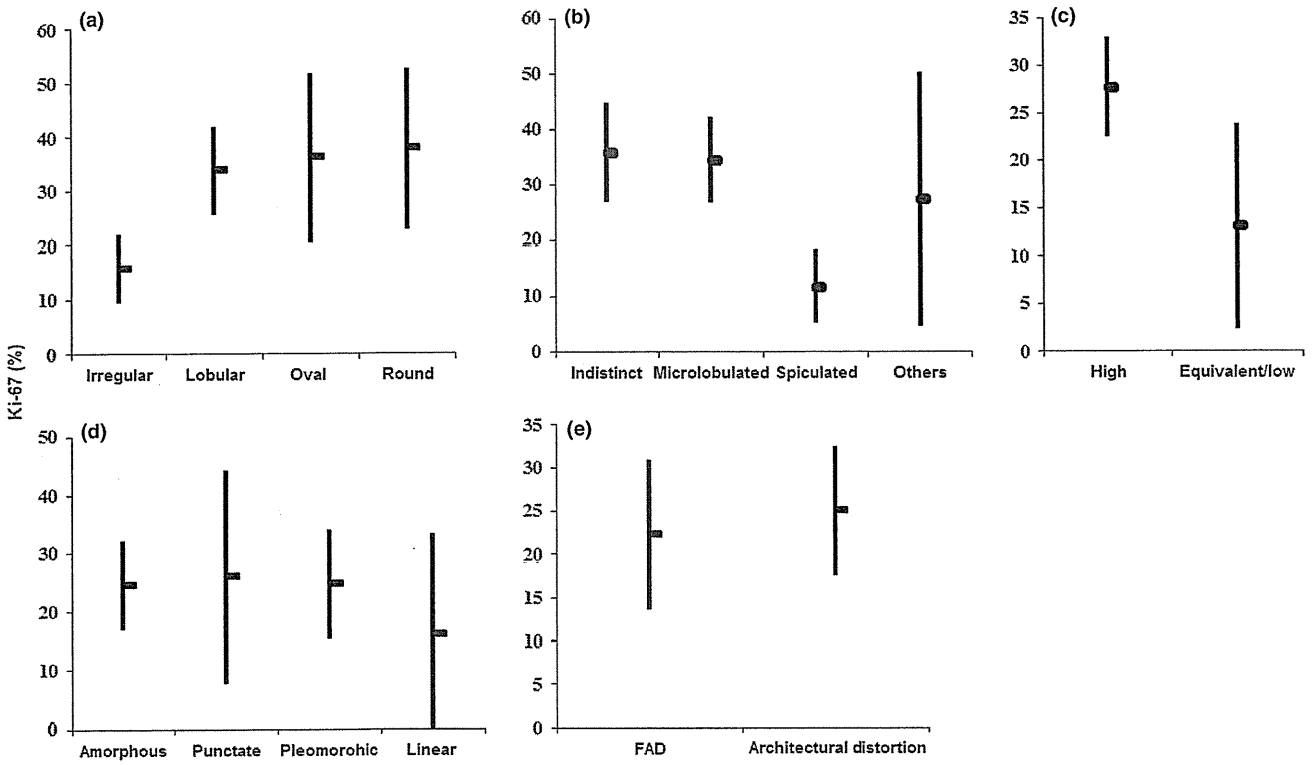

Fig. 5. Correlation between mammographic findings and Ki-67 labeling index: (a) mass shape, (b) margin, (c) density, (d) calcification shape, and (e) focal asymmetric density (FAD) and architectural distortion.

well-defined masses were associated with triple-negative breast cancer.[8,21] The results of the present study demonstrate that is a higher incidence of lower histological grade in masses with an irregular shape and/or spiculated margins, although a higher histological grade is not necessarily associated with irregular mass shape or spiculated margins. In addition, correlation of mammographic findings with the intrinsic subtype demonstrated that irregular mass shape and/or spiculated margin masses were significantly more frequently detected in luminal A breast cancers than in the other subtypes in this cohort of Japanese patients. However, oval and round mass shape and/or indistinct and microlobulated margin masses were significantly more frequently detected in triple-negative breast cancers or HER breast cancers. As for architectural distortion, the ratio of architectural distortion was significantly higher in luminal A cases and also tended to be associated with histological Grade 1. Together, these results suggest that poorly differentiated breast carcinoma cells are associated with good histological grade and luminal A subclassification. However, well-differentiated carcinoma cells are associated with adverse clinical grading and negative ER status.

Previous studies have demonstrated that these differentiations were related somewhat with adhesion factors.[22,23] Loss of adhesion factors in carcinoma cell is considered to play a role in the characteristic histological appearance of invasive carcinoma as loosely dispersed linear columns of cells and a typical discrete mass.[22] This more diffuse infiltrative pattern may explain some of the typical imaging appearances of tumors, such as spiculation and distortion.[22] In addition, adhesion factors are correlated with high histologic grade.[23] Therefore, adhesion factors may be considered to be correlated with the results of the present study in that spiculated breast cancers have a good clinical outcome and histological Grade 1. However, it is also true that numerous biological mechanisms underlying the association between the process of infiltration and histopathological characteristics remain unknown and that further investigations are required to confirm interpretation of mammography in terms of the biological and histopathologic characteristics of tumors.

To the best of our knowledge, this is the first study to compare mammographic findings with the Ki-67 labeling index and histopathological lymphovascular invasion. The results of the present study demonstrated that there was a higher incidence of a lower Ki-67 labeling index in tumors with an irregular mass shape, spiculated periphery, and equivalent or low mass density. Irregular mass shape and a spiculated periphery are well-known predictors of malignancy, but the results of the present study seem to suggest that findings of irregular shape and a spiculated periphery are relatively good prognostic predictors in terms of the Ki-67 labeling index. In addition, the results of the present study demonstrate that lymphovascular invasion was significantly greater in cases in which there was architectural distortion; however, the incidence of lymphovascular invasion was not significantly higher in spiculated masses. These results all suggest that the correlation between findings of radiological dist ortion and the mechanisms of lymphovascular invasion remain unknown and further investigations are required.

We also examined the correlation between mammographic calcification shape and histopathological characteristics. Previous studies have reported that triple-negative breast cancers are more likely to exhibit comedo calcifications.[8] In addition, the high frequency of comedo calcification in triple-negative breast cancers may represent a consequence of high histologic grade.[8] The presence of mammographic comedo calcification has also been reported to be associated with a poor prognosis in small screening-detected invasive cancers.[19] The results of the present study also demonstrate that non-necrotic calcifications, including amorphous and punctate calcification, are associated with a higher ratio of luminal A cases, whereas necrotic calcifications, including pleomorphic and linear calcification, were

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associated with a higher ratio of HER breast cancers. In addition, necrotic calcifications tended to be associated with a higher histological grade than non-necrotic calcifications. Therefore, the results suggest that the type of calcification may become a prognostic factor for breast malignancies.

We noted significant differences in the mammographic features of different primary breast cancer immunophenotypes in the present study. Stratifying the mammographic features according to immunophenotypes reveals distinct differences among cancer subtypes. However, the limitations of the present study include that fact that the study was retrospective in nature and was performed in a single institute, namely Tohoku University Hospital. Therefore, further investigations are needed, including analysis in several different institutions to further refine the new mammographic criteria. Biological and histopathological differences may result in imaging differences that may help us better understand the development of breast cancer. These proposed mammographic diagnostic criteria based on biological characteristics may contribute to a more accurate prediction of the biological behavior of breast malignancies.

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Disclosure Statement

The authors have no conflict of interest.

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Multidetector row helical computed tomography for invasive ductal carcinoma of the breast: Correlation between radiological findings and the corresponding biological characteristics of patients

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The aim of this study is to evaluate the correlation between multidetector row helical computed tomography (MDCT) findings and the histopathological characteristics of patients with invasive ductal carcinoma. We retrospectively reviewed MDCT findings and the corresponding histopathological features of 442 women with invasive ductal carcinoma. We received informed consent from the patients and the protocol was approved by the Ethics Committee at Tohoku University. The median age was 53 years (26–89 years). We examined the MDCT findings based on mass shape classified into well, moderate, poorly and scattered demarcated shapes, the enhancement pattern classified into homogenous, heterogeneous, rim and poor, and mass density classified into high, intermediate or low. We subsequently compared these radiological findings with the histological characteristics and clinical outcome. Poorly demarcated types were higher in ER+/HER2– ($P = 0.008$), while the well-demarcated type was higher in ER–/HER2– and ER–/HER2+ ($P < 0.001$ and $P = 0.010$). Rim pattern was higher in ER–/HER2– ($P < 0.001$). Intermediate or low density was higher in ER–/HER2– ($P < 0.001$, respectively). Further analysis based on histological grade, mitotic counts and lymphovascular invasion demonstrated that the well-demarcated shape was higher in grade 2 and 3 ($P = 0.006$ and $P < 0.001$, respectively), and rim pattern was observed in grade 3 ($P < 0.001$). Regarding mitotic counts, poorly and scattered demarcated shapes were observed in score 1 ($P = 0.008$ and $P = 0.014$), while well-demarcated shape and rim enhancement were observed in score 3 ($P < 0.001$, respectively). Lymphovascular invasion correlated with a moderate demarcated shape ($P = 0.029$). Regarding recurrence rates, there were statistically significant differences between well and moderate, poorly or scattered demarcated shapes ($P = 0.007$, 0.028 and 0.035, respectively). These proposed MDCT diagnostic criteria based on biological characteristics contribute to more accurately predicting the biological behavior of breast cancer patients. (*Cancer Sci* 2012; 103: 67–72)

Histological tumor type, grade, lymphovascular invasion and molecular markers such as estrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2) status are standard prognostic indicators in breast cancer patients.[1–3] This histological information can contribute to an optimal selection of treatment strategy including endocrine therapy, chemotherapy and targeted therapy in individual patients with breast cancer.[4,5] Several previous studies examined the correlation between radiological findings and the corresponding histopathological characteristics.[6–11] A number of independent studies demonstrated that spiculated periphery masses in mammography were associated with a good outcome, whereas well-defined masses were associated with triple-negative breast cancer cases.[7,8] In addition, a spiculated margin of breast cancer on high spatial resolution dynamic magnetic resonance imaging (MRI) was reported to be able to predict a lower histological grade.[9] As for ultrasonography, a poorly circumscribed margin, abrupt boundary and a hypoechoic or complex echo pattern were reported to be more frequent in grade 3 than in grade 1–2 invasive cancer cases.[10] Therefore, an accurate correlation of radiological findings with their corresponding histopathological features is considered one of the most important in imaging evaluation of breast malignancies, especially with reference to the study of biological features of the patients.

The recent development of multidetector row helical computed tomography (MDCT) has markedly improved the resolution that can be achieved in CT scanning, allowing the entire breast to be scanned in thin slices.[12,13] This instrument can detect much smaller lesions and provide more detailed information regarding the extent of breast cancer infiltration because of faster scanning, a wider area of scan coverage and higher resolution of the volume data than single helical CT.[12,13] However, to the best of our knowledge, no studies have reported on the correlation between these MDCT findings and the corresponding biological characteristics in individual patients with breast cancer. Therefore, in the present study, we evaluated the MDCT findings and compared the histological characteristics including ER, HER2 status, histological grade, mitotic counts of the cancer cells and lymphovascular invasion in a retrospective manner.

Materials and Methods

Patients. We retrospectively reviewed the MDCT findings and histopathological features of 442 invasive ductal carcinoma of the breast for which surgery was performed in Tohoku University Hospital in Sendai Japan from January 2005 to June 2010. We received informed consent from all patients and the protocol for the present study was approved by the Ethics Committee at Tohoku University Graduate School of Medicine. The median age of the patients was 53 years (range 26–89 years). Table 1 summarizes the patient characteristics.

Imaging devices and breast tissue specimens. The MDCT evaluations were performed using a 16-row detector CT system (Somatom Sensation Cardiac; Siemens Medical Solutions,

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Table 1. Patient characteristics

Patient age, median (range) (years)	53 (26–89)
Hormone receptor and HER2 expression	
ER+/HER2–	327
ER+/HER2+	29
ER–/HER2–	55
ER–/HER2+	31
Histological grade	
HG1	149
HG2	213
HG3	80
Mitotic counts of carcinoma cells	
Score 1	298
Score 2	72
Score 3	72
Lymphovascular invasion	
Ly+	220
Ly–	222

ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HG, histological grade; Ly, lymphovascular invasion; +, positive; –, negative.

Table 2. Definition of MDCT findings

	Definition
Tumor shape	
Well demarcated	Oval mass shape and circumscribed periphery
Moderate demarcated	Mixed contour of well and poorly demarcated shape
Poorly demarcated	Irregular mass shape and spiculated periphery
Scattered demarcated	Lesion with multiple spotted foci
Enhancement pattern	
Homogenous	Diffuse and monotonous enhancement pattern
Heterogenous	Mosaic pattern
Rim	Enhancement only in periphery of the tumor
Poor	Weak enhancement
Density	
High	High density compared with the normal mammary gland
Intermediate or low	Equal or low density compared with the normal mammary gland

MDCT, multidetector row helical computed tomography.

Erlangen, Germany). A total of 2 mL/kg of nonionic iodine contrast materials (300 mg I/mL) was injected at a rate of 2.0 mL/s. The CT data acquisition started 60 s after commencing the injection of contrast medium. We used an X-ray tube modulation system (CARE Dose 4D; Siemens Medical Solutions). The X-ray tube voltages were 80, 100 or 120 kV and the quality reference tube current-time product was set at 120 mAs. The CT was performed in a craniocaudal direction with a section thickness of 0.75 mm and a table feed of 12 mm per rotation, resulting in a pitch factor of 1. The gantry rotation time was 0.5 s. Transverse CT images were reconstructed using a section thickness and increment of 1 mm each. The additional reconstruction was achieved by targeting the relevant side of the breast with the same thickness and increment. All data were sent to the Advantage Workstation v4.1/4.2 (GE Healthcare, Milwaukee, WI, USA).

The slides of the cases were stained with hematoxylin–eosin (HE) and immunohistochemical antibody for ER and HER2. Surgical specimens had been fixed in 10% formaldehyde solution and cut into serial 5-mm-thick slices, embedded in paraffin, cut into 4-μm-thick sections, and placed on the glue-coated glass slides. We used the avidin–streptavidin immunoperoxidase method using the clone 6F11 antibody (Ventana, Tucson, AZ, USA) in an automated immunostainer (Benchmark System; Ventana). A standardized immunohistochemistry kit (Hercep-Test for Immunoenzymatic Staining; Dako, Copenhagen, Denmark) was used for HER2 staining.

Imaging and histopathological analyses. Two experienced breast physicians and one experienced radiologist independently evaluated the MDCT findings of all cases examined in the present study. These three investigators were blinded to the histopathological diagnosis and the clinical outcome of the patients. If there were discrepancies between the investigators, they reached a final decision using consensus evaluations from eight experienced breast physicians and radiologists. We recorded tumor shape, enhancement pattern and density. Table 2 summarizes the definition of MDCT findings. Tumor shape was defined on the basis of gross tumor configuration from stellate to circumscribed, and tentatively classified into a well-demarcated shape including an oval mass shape and circumscribed periphery, a poorly demarcated shape including an irregular mass shape and spiculated periphery, a moderate demarcated shape having a mixed contour and a scattered demarcated shape (Fig. 1). The enhancement pattern was tentatively classified into homogenous, heterogenous, rim and poor enhancement (Fig. 1). Density of the lesion after injection of contrast media was subsequently compared with that of normal mammary gland and tentatively classified into high and intermediate or low (Fig. 1).

Two of the experienced pathologists independently evaluated the surgical pathology specimens, respectively. Histopathological evaluation was based on the World Health Organization histological classification of tumors of the breast and *Rosen's Breast Pathology*.[14,15] Estrogen receptor was determined by nuclear staining graded from 0 to 8 using the Allred score, and positive was grade 3 or more.[16] With regard to HER2 evaluation, membranous staining was graded as follows: score 0–1+, 2+ and 3+.[17] Scoring of 2+ cases were added in the other examination of fluorescence *in situ* hybridization (FISH) that was used to calculate the gene copy ratio of HER2-to-CEP17 (PathVysion HER2 DNA Probe kit; Abbott, Chicago, IL, USA). Positive was defined as either HER2 : CEP17 signal ratio (FISH score) >2.2.[17] Histological grades and mitotic counts were assessed according to the criteria of Elston and Ellis.[2] We also identified the presence or absence of lymphovascular invasion according to *Rosen's Breast Pathology*.[15]

We examined the MDCT findings including tumor shape, enhancement pattern and density with the histopathological characteristics including ER, HER2 status, histological grade, mitotic counts and lymphovascular invasion. In addition, we examined the correlation between MDCT findings and clinical outcome including recurrence rate and recurrence-free survival of the patients.

Statistical analysis. To compare the MDCT findings with the histopathological findings, multivariate statistics were used. All analyses were performed with the use of statistical software (SPSS, version 10.0; SPSS, Chicago, IL, USA), with $P < 0.05$ indicating a significant difference.

Results

Comparison of MDCT findings with ER and HER2 status. Table 3 summarizes the results of the numbers and ratios of each MDCT findings according to ER and HER2 status. There were statistically higher cases of moderate and poorly in the

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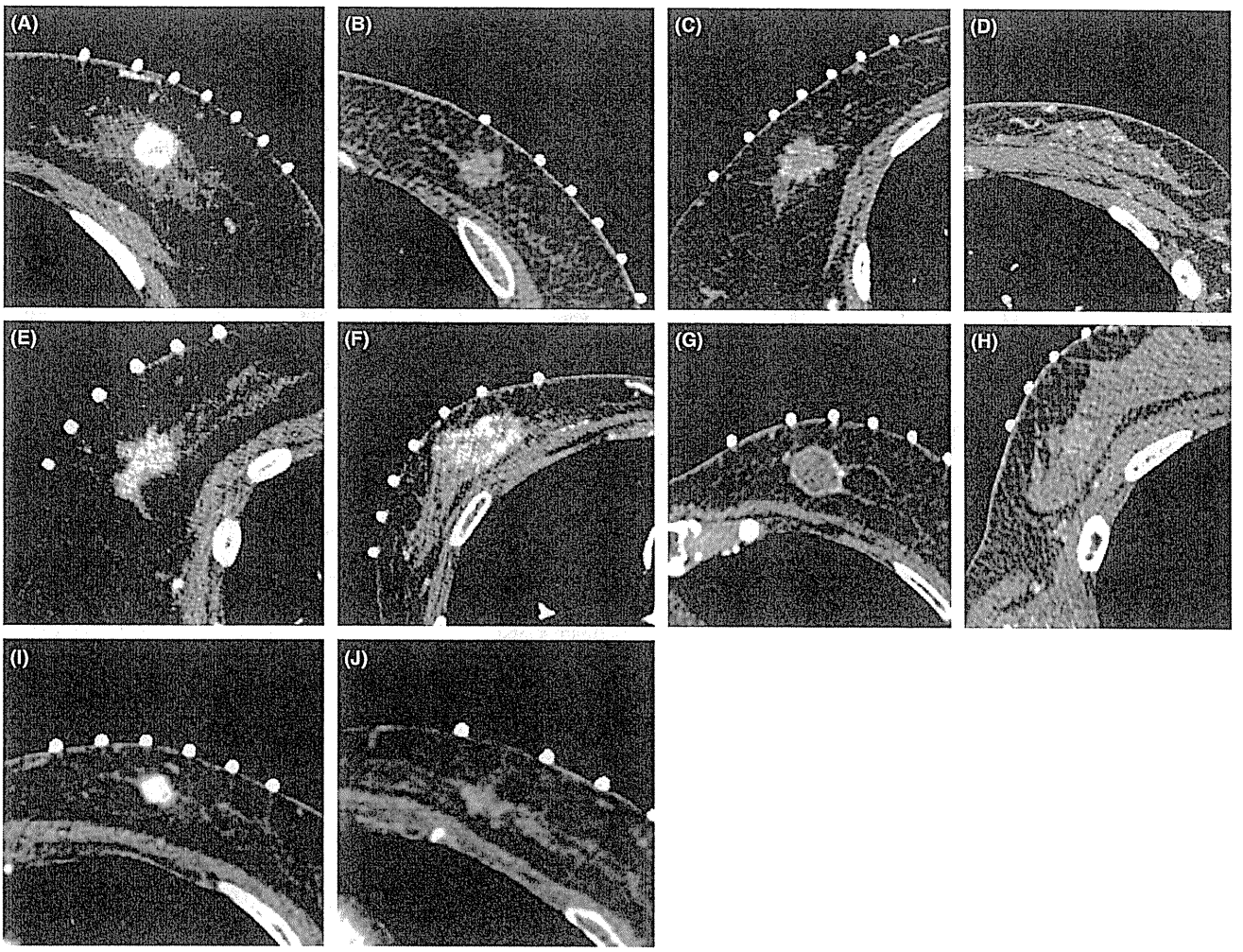

Fig. 1. Representative images of tumor shape, enhancement pattern and density according to multidetector row helical computed tomography findings. (A) Well-demarcated shape, (B) moderate demarcated shape, (C) poorly demarcated shape, (D) scattered demarcated shape, (E) homogenous enhancement pattern, (F) heterogenous pattern, (G) rim pattern, (H) poor enhancement, (I) high density and (J) intermediate or low density.

ER+/HER2− group ($P = 0.014$ and $P = 0.008$, respectively), well in the ER−/HER2− group ($P < 0.001$) and well in the ER−/HER2+ group ($P = 0.010$). However, there were statistically lower ratios of well-demarcated shape compared with other tumor shapes in the ER+/HER2− group ($P < 0.001$) and of poorly in the ER−/HER2− group ($P = 0.004$). Regarding enhancement patterns and density, there were statistically higher cases demonstrating rim pattern and/or intermediate and low density in the ER−/HER2− group ($P < 0.001$, respectively). However, there were statistically lower ratios of rim in the ER+/HER2− group ($P < 0.001$) and of homogenous pattern in the ER−/HER2− group ($P = 0.014$), and of high density in the ER−/HER2− group ($P < 0.001$) (Table 3).

Comparison of MDCT findings with histological grades. Table 4 summarizes the results of the numbers and ratios of each MDCT finding according to histological grade. As for mass shape, there was a statistically higher ratio of well in the grade 3 group ($P < 0.001$) and poorly in the grade 1 group ($P = 0.012$), whereas lower ratios of well in the grade 1 and grade 2 groups ($P < 0.001$ and $P = 0.006$) and moderate and poorly in the grade 3 group ($P = 0.010$ and $P < 0.001$). Regarding the enhancement pattern, there were statistically higher ratios of homogenous in the grade 1 group ($P = 0.041$) and of rim pattern in the grade 3 group ($P < 0.001$). However, there was a statistically lower ratio of homogenous in the grade 3 group ($P = 0.020$) and of rim pattern in the grade 1 group ($P < 0.001$). There was no statistical significance in the correlation between histological grade and density (Table 4).

Comparison of MDCT findings with mitotic counts. Table 5 summarizes the results of the numbers and ratios of each MDCT finding according to mitotic counts. There were statistically higher ratios of poorly in the score 1 group ($P = 0.008$), well in the score 3 group ($P < 0.001$) and scattered in the score 1 group ($P = 0.014$), whereas lower ratios of well-demarcated shape in the score 1 group ($P = 0.015$) and poorly demarcated shape in the score 3 group ($P = 0.007$). As for the enhancement pattern, there were higher ratios of rim pattern in the score 2 and score 3 groups ($P = 0.004$ and $P < 0.001$, respectively) and poor pattern in the score 1 group ($P = 0.027$), whereas a lower ratio of rim pattern in the score 1 group ($P < 0.001$). There was no statistical significance in the correlation between mitotic counts and density (Table 5).

Comparison of MDCT findings with lymphovascular invasion. Table 6 summarizes the results of the numbers and ratios of each MDCT finding according to lymphovascular invasion. There was a statistically higher ratio of lymphovascular

Table 3. Comparison of MDCT findings with ER and HER2 status

	ER+/HER2−	ER+/HER2+	ER−/HER2−	ER−/HER2+
Tumor shape				
Well	23	5	24*	9*
Moderate	169*	12	20	13
Poorly	110*	8	8	8
Scattered	25	4	5	1
Enhancement pattern				
Homogenous	142	10	14	14
Heterogenous	162	16	26	15
Rim	8	2	12*	2
Poor	15	1	3	0
Density				
High	198	21	20	22
Intermediate/low	129	8	35*	9

*Higher ratio $P < 0.05$. ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; MDCT, multidetector row helical computed tomography; +, positive; −, negative.

Table 4. Comparison of MDCT findings with histological grade

	Grade 1	Grade 2	Grade 3
Tumor shape			
Well	3	19	38*
Moderate	75	109	28
Poorly	61*	72	13
Scattered	10	13	1
Enhancement pattern			
Homogenous	72*	88	24
Heterogenous	76	103	35
Rim	1	13	19*
Poor	0	9	2
Density			
High	92	127	48
Intermediate/low	57	86	32

*Higher ratio $P < 0.05$. MDCT, multidetector row helical computed tomography.

Table 5. Comparison of MDCT findings with mitotic counts

	Score 1	Score 2	Score 3
Tumor shape			
Well	27	15	28*
Moderate	142	33	31
Poorly	103*	22	9
Scattered	28*	2	2
Enhancement pattern			
Homogenous	127	26	21
Heterogenous	147	31	31
Rim	4	14*	16*
Poor	22*	1	2
Density			
High	183	46	38
Intermediate/low	115	26	34

*Higher ratio $P < 0.05$. MDCT, multidetector row helical computed tomography.

Table 6. Comparison of MDCT findings with lymphovascular invasion

	Ly+	Ly−
Tumor shape		
Well	36	26
Moderate	113*	91
Poorly	62	72
Scattered	9	33
Enhancement pattern		
Homogenous	82	92
Heterogenous	110	99
Rim	19	11
Poor	9	20
Density		
High	139	128
Intermediate/low	81	94

*Higher ratio $P < 0.05$. Ly, lymphovascular invasion; MDCT, multidetector row helical computed tomography; +, positive; −, negative.

invasion in the moderate demarcated shape group ($P = 0.029$). However, there were statistically lower ratios of lymphovascular invasion in the scattered and/or poor enhancement pattern ($P < 0.001$ and $P = 0.037$) (Table 6).

Comparison of MDCT findings with clinical outcome of the patients. Disease recurrence rates according to tumor shape were 25.0% in the well-demarcated shape, 6.7% in the moderate demarcated shape, 8.8% in the poorly demarcated shape and 0% in the scattered demarcated shape. There were statistically significant differences between well and moderate, poorly or scattered demarcated shapes ($P = 0.007$, 0.028 and 0.035, respectively). Recurrence rates according to enhancement pattern were 5.7% in homogenous, 10.6% in heterogenous, 20.0% in rim and 9.1% in the rim enhancement pattern. There were no statistically significant differences according to enhancement patterns. Recurrence rates according to density were 9.0% in high and 8.9% in intermediate or low density and there were no statistically significant differences between these two groups. Figure 2 shows the recurrence-free survival in relation to tumor shape and enhancement patterns according to the Kaplan–Meier method. There were statistically significant differences between the well-demarcated shape and the moderate or scattered demarcated shape ($P = 0.024$ and 0.038, respectively).

Discussion

Breast cancer is a disease associated with heterogeneous outcomes and numerous studies have been reported regarding the establishment of prognostic factors of individual patients. Traditional prognostic factors that were correlated with the overall survival of patients include histological grade, mitotic counts and lymphovascular invasion of individual cases.[2,18] Several molecular prognostic factors including ER and HER2 status have over the past few years been clearly demonstrated to contribute significantly to the management and subsequent prognosis of patients with breast cancer.[18,19] Therefore, an accurate correlation of radiological findings with their corresponding histopathological features is considered most important in the radiological evaluation of patients with breast cancer. In addition, the recognition of how many radiological features obtained might actually reflect the prognosis of individual patients is considered markedly important in gaining insight into how the tumor proliferates and into potentially determining which tumors can be managed with aggressive adjuvant treatment. The purpose of the present study is therefore to evaluate the correlation of MDCT findings including tumor shape, enhancement pattern and density with ER expression, HER2 status, histological grade, mitotic counts and lymphovascular invasion in Japanese patients with breast cancer.

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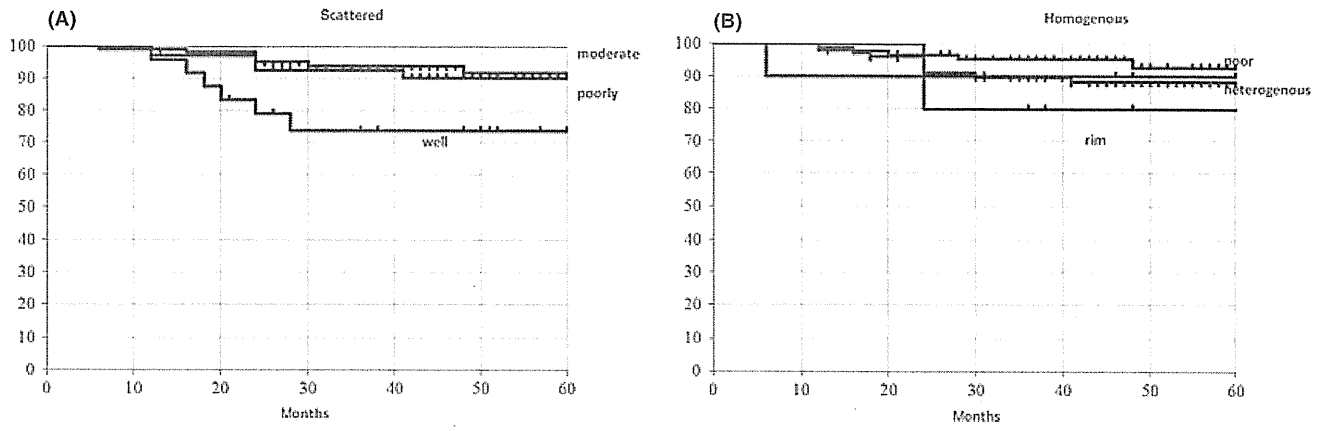

Fig. 2. Recurrence-free survival according to multidetector row helical computed tomography findings using the Kaplan–Meier method. (A) Tumor shape and (B) enhancement pattern.

Several previous studies evaluated the correlation between radiological findings including mammography, ultrasonography and MRI and histopathological characteristics of individual patients.[7–11,20] For mammography, a number of independent study groups demonstrated that spiculated periphery masses were significantly associated with a good outcome for patients,[7,8] but well-defined masses were associated with triple-negative breast cancer.[7,8] Previous studies also compared the ultrasonographic findings of ER-negative/HER2-negative cancers with those of ER-negative/HER2-positive cancers and concluded that ER-negative/HER2-positive breast cancers were likely to demonstrate spiculated margins and to be associated with calcifications.[10] In addition, ER-negative/HER2-negative breast cancers were more likely to show as smooth or circumscribed masses.[10] A spiculated margin in MRI findings did demonstrate an association with positive ER expression and negative HER2 status, and high-grade malignant breast cancers circumscribed margins.[9,20]

Results of the present study did demonstrate that there was a higher incidence of increased ratios of ER+/HER2− type, lower histological grade, lower mitotic counts and a lower ratio of lymphovascular invasion in poorly demarcated masses, whereas the presence of higher ratios of triple-negative type, higher histological grade, higher mitotic counts and lymphovascular invasion were all demonstrated to be associated with well-demarcated masses in the present study. In addition, these results all suggest that poorly demarcated breast cancer was associated with a good clinical outcome, and well-demarcated shape of carcinoma cells was associated with an adverse clinical outcome and negative ER status in carcinoma cells. Results of the present study were similar to those of previously reported studies regarding the correlation between mammography or MRI findings and intrinsic subtype or histological grade of cases.[7–11,20] Inoue *et al.*[21] reported the correlation between MDCT findings and the ratio of malignant cases but they did not necessarily focus on the histopathological characteristics of the cases examined. Therefore, to the best of our knowledge, this is the first study to examine the correlation between MDCT findings and the corresponding histopathological features. However, the mechanisms of the correlation between intrinsic subtype or histological grade and the growth pattern of carcinoma cells have not been elucidated. Therefore, further studies are required to investigate the potential mechanisms of correlation between biological characteristics and the growth pattern of carcinoma cells.

Results of the present study also demonstrated that there were statistically significant correlations of rim enhancement patterns with triple-negative breast cancer and higher histological grade. Rim enhancement was one of the important morphological signs in predicting the worse clinical outcomes. These results all suggest that high angiogenesis might be present in the peripheral lesion of the masses and central necrosis and fibrosis. A previous MRI study also demonstrated the correlation between rim enhancement and large tumor size, higher histological grade or negative hormone receptor status of cases.[22] However, this is the first study examining the correlation between rim enhancement in MDCT findings and biological characteristics of breast malignancies. In general, rim enhancement is more frequently noted in rapidly growing breast carcinomas.

In addition, we also examined the recurrence ratio and recurrence-free survival of patients according to MDCT findings. Results of the present study demonstrated that a well-demarcated shape was associated with a significantly higher recurrence ratio than other groups ($P = 0.007$, 0.028 and 0.035, respectively). A similar tendency was also detected in the rim enhancement pattern but the difference did not reach statistical significance. Therefore, MDCT findings of well-demarcated shape and rim enhancement pattern can become one of the predictors of a worse clinical outcome for patients.

We noted significant differences in the MDCT features of different primary breast cancer types in the present study. Stratifying the MDCT features according to phenotypes reveals distinct differences among cancer subtypes. However, the present study was retrospective and examined in a single institute. Therefore, it is probable that further investigation of not only Japanese women but also other Asian women will confirm the new MDCT criteria. Biological and histopathological differences may result in the imaging differences that might help us better understand breast cancer development. These proposed MDCT diagnostic criteria based on biological characteristics might provide a more accurate prediction of biological behavior of breast malignancies when radiologists evaluate the findings of MDCT.

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Disclosure Statement

The authors have no conflict of interest.