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Report

Usefulness of three-dimensional multidetector-row CT images for preoperative evaluation of tumor extension in primary breast cancer patients

Tomoo Inoue[1], Yasuhiro Tamaki[1], Seiki Hamada[2], Shuji Yamamoto[2], Yoshinobu Sato[3], Shinichi Tamura[3], Seung Jin Kim[1], Yoshio Tanji[1], Yasuo Miyoshi[1], Tetsuya Taguchi[1], and Shinzaburo Noguchi[1]

[1]*Department of Surgical Oncology;* [2]*Department of Radiology, Osaka University Graduate School of Medicine;* [3]*Division of Interdisciplinary Image Analysis, Department of Medical Robotics and Image Sciences, Osaka University Graduate School of Medicine, Yamadaoka, Suita, Osaka, Japan*

Key words: breast cancer, tumor size, multidetector-row CT

Summary

Purpose: Usefulness of three dimensional (3D) multidetector-row CT (MDCT) images for preoperative evaluation of tumor extension was studied in primary breast cancer patients.

Methods: 3D-MDCT tumor images of 143 tumors in 143 patients with primary breast cancer were created with the volume rendering method. The transverse tumor size (TS) and vertical tumor size (VS) were then measured in an anterior-posterior view of the 3D-MDCT images. The pathological tumor size was determined according to a map of the tumor spread prepared by pathologists using multi-sliced (3–5 mm intervals) surgical specimens and compared with the tumor size on 3D-MDCT images.

Results: First, the optimal method for creating 3D-MDCT tumor images was determined for the first 40 patients (learning set), resulting in a fairly good correlation of tumor size on 3D-MDCT images with pathological tumor size ($r = 0.983$ for TS and $r = 0.958$ for VS). We then carried out a validation study on the next 103 patients (validation set). The 3D-MDCT tumor size's strong correlation with the pathological tumor size demonstrated a high rate of accuracy ($r = 0.974$ for TS and $r = 0.977$ for VS). Subset analyses according to histological type showed that correlation coefficients were $r = 0.979$ for TS and $r = 0.981$ for VS of invasive ductal carcinomas ($n = 88$), $r = 0.948$ for TS and $r = 0.970$ for VS of ductal carcinomas *in situ* ($n = 10$), and $r = 0.984$ for TS and $r = 0.976$ for VS of invasive lobular carcinomas ($n = 5$).

Conclusion: 3D-MDCT images can assess breast cancer tumor extension highly accurately, and thus seems to be useful for planning the extent of resection in breast conserving surgery.

Introduction

Complete removal of a breast tumor with its tumor-negative surgical margins is most important for avoiding local recurrence (ipsilateral in-breast recurrence) in breast conserving surgery [1–3]. Wider excision of the breast gland can result in a lower risk of local recurrence but produces a poorer cosmetic outcome. To cope with the dual problem of curability and cosmetic outcome, preoperative, accurate assessment of tumor extension is of vital importance. For this purpose, many studies have been conducted using a variety of imaging modalities, i.e., mammography, ultrasonography (US), magnetic resonance imaging (MRI), and helical computed tomography (helical CT) [4–20]. However, none of these modalities is sensitive enough to visualize intraductal spreading of the tumor or small daughter nodules with satisfactory accuracy [5, 8, 14, 16, 17]. It is thus often difficult to predict precisely the extension of an invasive ductal carcinoma associated with extensive intraductal spreading or of a ductal carcinoma *in situ* (DCIS), as well as the extension of a multifocal invasive lobular carcinoma (ILC) [21–23]. MRI can visualize intraductal spreading with a higher accuracy than other imaging modalities but has the disadvantage that images are obtained with the patient in the prone position whereas the surgery is done with the patient in the supine position (the breast easily changes shape with a change in position). Recently, multidetector-row CT, which provides high-quality, high-resolution 3D images, has been used for preoperative evaluation of tumor extension in various malignant diseases. While promising results have been reported [24–28], no results for breast cancer have been reported yet. Much useful software for 3D image analysis has become available on personal computers. This recent technological development has facilitated the construction and handling of 3D images as well as their precise analysis. MDCT, because of its high resolution, is expected to make it possible to visualize tumor extension with a high degree of accuracy. MDCT has the

additional advantage over MRI that it can be performed with the patient in a supine position similar to the position used during surgery. These reported results and characteristics prompted us to evaluate the usefulness of MDCT for the preoperative evaluation of breast tumor extension by comparing the tumor size determined with the aid of 3D-MDCT images with the pathologically determined tumor size.

Materials and methods

Patients

Primary breast cancer patients, who were clinically considered eligible for breast conserving surgery, were first given an MDCT examined and then underwent breast conserving surgery or mastectomy between June 2001 and April 2004 at Osaka university Hospital. Patients who had undergone preoperative excisional biopsy and/or neoadjuvant chemotherapy were excluded from this study. Informed consent was obtained from all patients. Eventually, 143 patients with unilateral breast cancer were included in the study. In the case of breast conserving surgery, additional resection of the breast tissue was performed if the margin was pathologically positive, so that eventually all the patients treated with breast conserving surgery showed negative margins. All surgical specimens were fixed and cut into 3–5 mm-thick slices perpendicularly to the line connecting the nipple and the center of the tumor. They were then examined microscopically by pathologists to produce a pathological map of the tumor extension.

Image acquisition by MDCT

Patients were examined in the supine position and with a 0.5-s four-slice MDCT (Aquilion-V detector; Toshiba Medical Systems Co., Tokyo, Japan). Target helical scanning (200 mm) of breast lesions was performed within a single breath-hold with 1 mm detector raw collimation and a helical pitch of 6:1 after pre-enhanced scanning of the whole thoracic area (300 mm) for breast cancer screening. This was followed by contrast enhanced scanning with biphasic helical CT scanning, for which 100 ml of nonionic contrast material, Iohexol 300™ (Daiichi Pharmaceutical Co., Ltd., Tokyo, Japan), was injected intravenously at a flow rate of 2.0 ml/s. The scanning was started when the peak aortic enhancement at the same slice level as the breast lesion reached 200 Hounsfield Units (HU) [29].

Creation and modification of 3D-MDCT images

The Digital Image and Communication in Medicine (DICOM) images of MDCT were transferred to a workstation, and 3D-MDCT images were created with the volume rendering method using Virtual Place™ 3D-image analysis software (Medical Imaging Laboratory Inc., Tokyo, Japan). For accurate tumor segmentation, the breast gland was selected as a region of interest (ROI) from an original 3D-MDCT image using multiplanar reformation (MPR) images. The tumor image was then displayed by controlling the opacity level according to the HU values of each pixel and rotated until eventually an anterior–posterior (A–P) view of the 3D volume image of the breast gland was obtained. The initial 40 patients served to determine the optimal

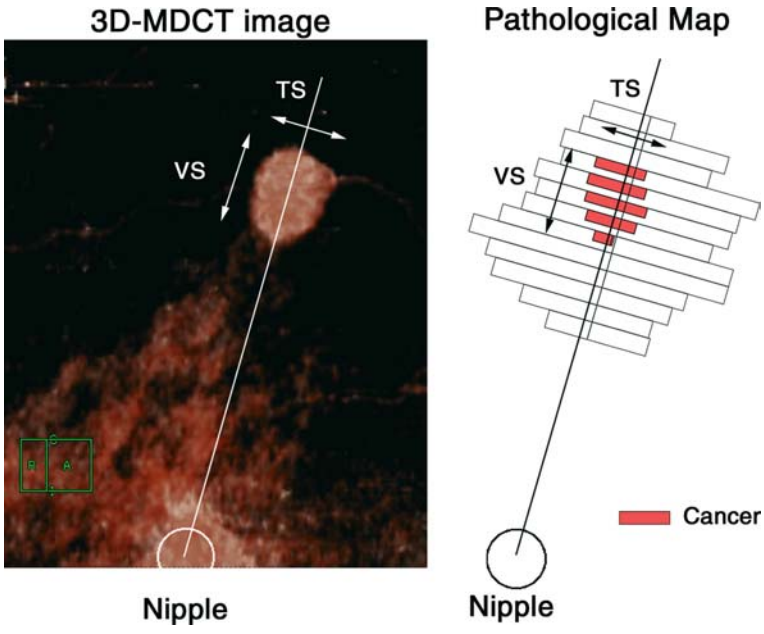

Figure 1. Measurement of tumor size on 3D-MDCT image and pathological map. Tumor size was measured in two directions, transverse size (TS) and vertical size (VS), in an A–P view of the 3D-MDCT image and on a pathological map created by pathological examination of sliced (3–5 mm intervals) surgical specimens.

opacity function condition and the optimal setting of the color map for the 3D-MDCT images so that these images showed good correspondence with the pathological map of tumor extension (learning set). Under these optimal conditions, 3D-MDCT tumor images were created for the next 103 patients (validation set), and the tumor size on the 3D-MDCT images was compared with pathological tumor size.

Measurement of tumor size

Tumor size was measured with Virtual Place™ software (Medical Imaging Laboratory Inc.) on A-P views of the 3D-MDCT volume images. The size was recorded at two rectangular directions, i.e., the transverse size (TS) parallel and the vertical size (VS) perpendicular to the slice of the pathological specimen (Figure 1). When spotty or linear augmentations were observed around the main tumor, the 3D-MDCT images were observed in more detail by rotating and slicing them at various angles to determine whether these augmentations were cancer nests. The pathological tumor size was measured in the same directions (TS and VS) with the aid of a pathological map of the tumor extension.

Statistical analysis

Tumor size determined by means of 3D-MDCT images and of pathological maps was compared by using Pearson's correlation coefficient test. All statistical analyses were performed with StatView™ software (SAS Institute Inc., Cary, NC).

Results

Patient characteristics and representative 3D-MDCT images

Patient characteristics of the learning set ($n = 40$) and validation set ($n = 103$) were not significantly different (Table 1). Representative 3D-MDCT images are shown in Figure 2. Figure 2A shows a case of invasive ductal carcinoma (IDC) located in the upper-inner quadrant of the right breast. The planar view of the 3D-MDCT image shows a good concordance with the pathological finding. A case of IDC with intraductal spreading is shown in Figure 2B. Pathological examination found small intraductal lesions near the main invasive tumor which were successfully visualized on the planar view of the 3D-MDCT image. Figure 2C shows a case of DCIS with extension under the nipple clearly visualized on the 3D-MDCT image.

Table 1. Patients characteristics in the learning set and validation set

	Learning set (n = 40)	Validation set (n = 103)
Age (average)	22–83 (53.7)	30–75 (51.7)
Menopausal status		
Pre menopausal	17	54
Post menopausal	23	49
Histological type		
IDC	35	88
ILC	2	5
DCIS	3	10
Tumor size (cm)		
≤2	25	53
2<, ≤5	15	50
Estrogen receptor		
Positive	34	78
Negative	6	25
Surgery		
BCS	24	55
Mastectomy	16	48

BCS – breast conserving surgery; DCIS – ductal carcinoma *in situ*; IDC – invasive ductal carcinoma; ILC – invasive lobular carcinoma.

Correlation of tumor size between 3D-MDCT and pathology

Tumor size obtained with an A–P view of 3D-MDCT images was compared with pathologically determined

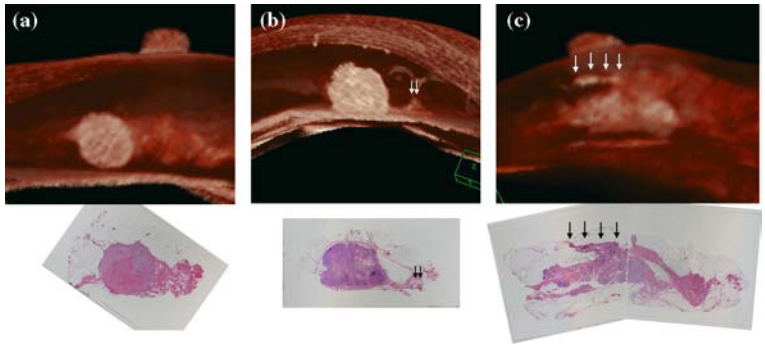

Figure 2. (A) A case of invasive ductal carcinoma without intraductal spreading in the upper-inner quadrant of the right breast. (B) A case of invasive ductal carcinoma with intraductal spreading in the upper-outer quadrant of the right breast. (C) A case of ductal carcinoma *in situ* with intraductal spreading under the nipple. Arrows in Figure 2B and C indicate the intraductal spreading of cancer cells.

tumor size in 143 tumors from 143 breast cancer patients. For the initial 40 patients (learning set) the correlation of tumor size obtained from 3D-MDCT images and pathologically determined tumor size was fairly good ($r = 0.983$ for TS and $r = 0.958$ for VS). The subsequent validation study using 103 patients (validation set) produced a high degree of correlation ($r = 0.974$ for TS and $r = 0.977$ for VS). Of these 103 tumors, five showed a difference in tumor size of more than 20 mm between the two methods (Figure 3). These tumors consisted of two IDC, two DCIS and one ILC. Subset analysis according to histological type showed that correlation coefficients were $r = 0.979$ for TS and $r = 0.981$ for VS of invasive ductal carcinomas ($n = 88$), $r = 0.948$ for TS and $r = 0.970$ for VS of ductal carcinomas *in situ* ($n = 10$), and $r = 0.984$ for TS and $r = 0.976$ for VS of invasive lobular carcinomas ($n = 5$) (Figure 4).

Since tumors with intraductal tumor spreading are reportedly difficult to visualize accurately with a variety of imaging modalities [5, 8, 14, 16, 19], tumor size obtained from the 3D-MDCT images was compared with pathologically determined tumor size only in the case of IDC tumors ($n = 57$) with intraductal spreading extending more than 5 mm from the invasive lesion. The correlation of the two modes of tumor size determination remained very good (0.978 for TS and 0.981 for VS), and only two tumors (3.5%) showed a difference of more than 20 mm between the tumor size obtained from 3D-MDCT and from pathological examination (Figure 5).

Discussion

A variety of imaging modalities has been used for examining tumor extension and multifocality in breast cancer patients since the diagnosis of these two features is very important for deciding whether breast conserving surgery is indicated. Mammography and ultrasonography are the first choice for screening and diagnosis of breast cancer. However, mammography has very limited value for premenopausal women with dense breasts and ultrasonography is not reliable enough to visualize tumor extension when the tumor contains extensive intraductal spreading [17, 30]. In breast conserving surgery, accurate identification of the tumor extension is very important for minimizing local recurrence resulting from incomplete resection of the tumor. These two conventional imaging modalities, however, are not sufficiently accurate for a precise evaluation of tumor extension in the breast. For this reason, MRI of the breast has recently been attracting much attention because its sensitivity for detecting breast lesions is so high that it can visualize the intraductal lesions around the main lesion with a high degree of accuracy [14, 17]. However, MRI has the disadvantage that it is usually performed with the patient in the prone position while the surgery is performed with the patient in the supine position. This means that MRI images of the breast are not so useful for the surgeon to plan the resection line for breast surgery because the breast easily changes shape with a change in position.

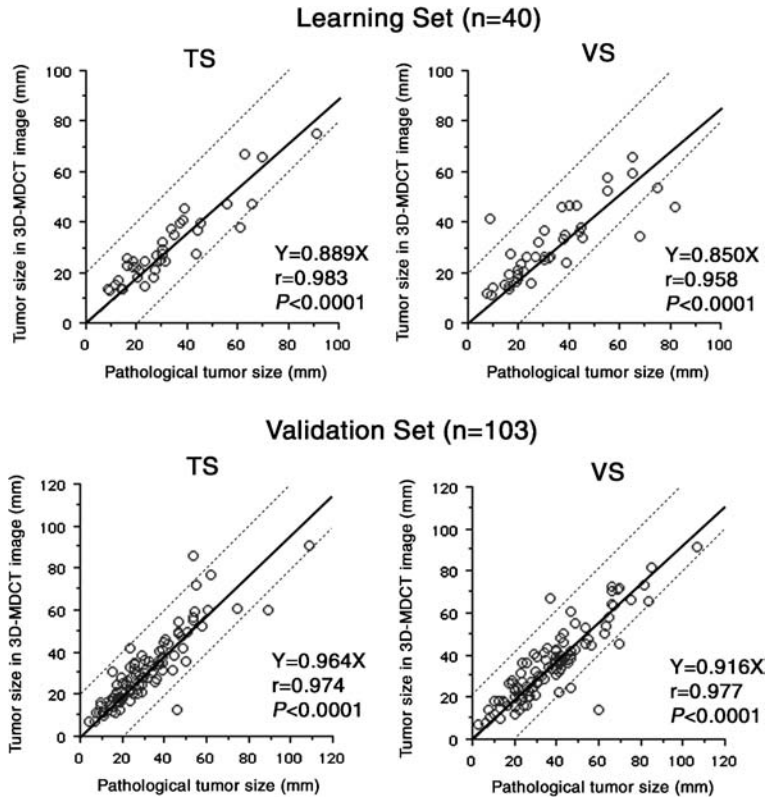

Figure 3. Relationships between tumor size obtained from 3D-MDCT images and pathologically determined tumor size for the learning set ($n = 40$) and the validation set ($n = 103$). Solid lines indicate regression coefficients and dotted lines indicate a 2 cm difference between the tumor sizes determined with the two modalities.

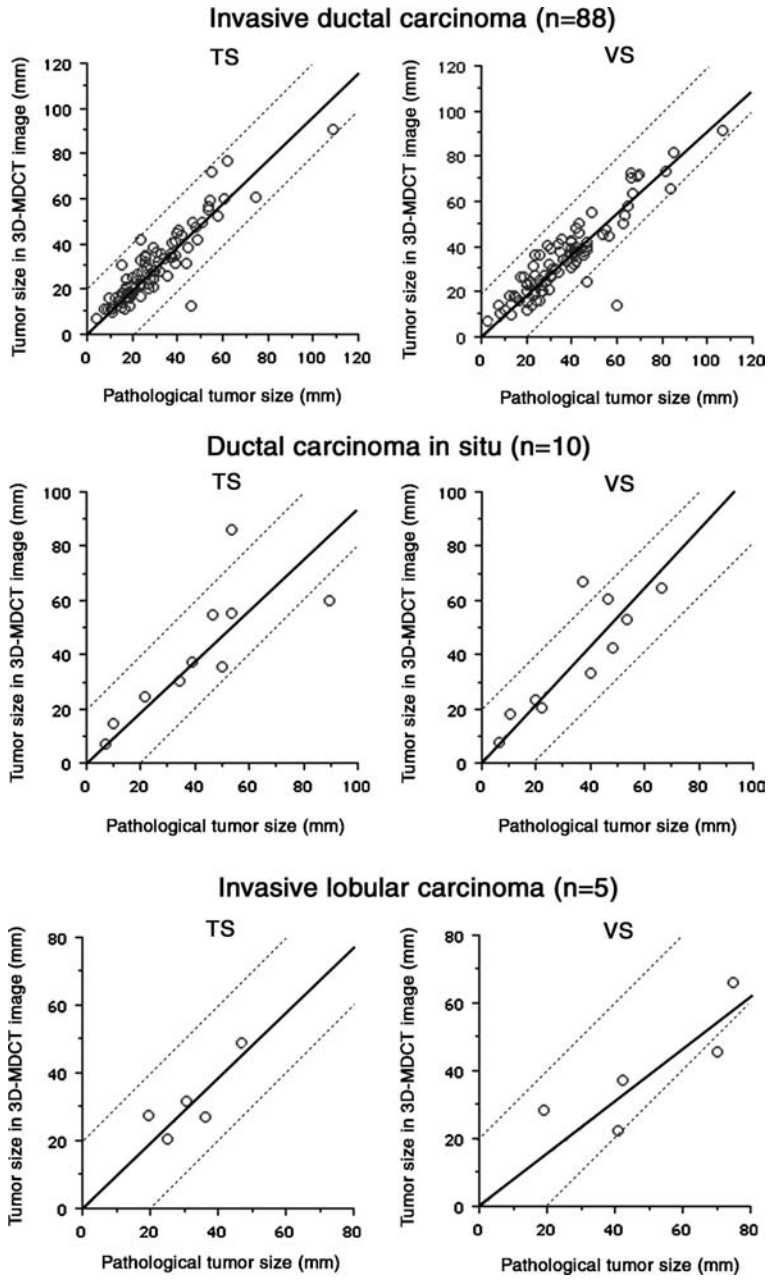

Figure 4. Relationship between tumor size obtained from 3D-MDCT images and pathologically determined tumor size for invasive ductal carcinomas ($n = 88$), ductal carcinomas *in situ* ($n = 10$), and invasive lobular carcinomas ($n = 5$). Solid lines indicate regression coefficients and dotted lines indicate a 2 cm difference between the tumor sizes determined with the two modalities.

Recent reports have described the usefulness of helical CT images of the breast [5, 6, 14, 16, 19]. Uematsu et al. reported that 3D-helical CT images of breast cancer obtained with the shaded surface display method were useful for the planning of breast conserving surgery. However, the sensitivity of helical CT images for detection of intraductal lesions was lower than that of MRI although its specificity was higher [14, 16]. One way to visualize such small lesions is to improve the spatial and contrast resolutions of the image. For this reason, MDCT is expected to provide more precise and accurate information of tumor spread in the breast.

In our study, we first determined the optimal procedure for creating 3D-MDCT tumor images by comparing the tumor size obtained from 3D-MDCT images with the pathologically determined size for the first 40 patients who made up the learning set. The tumor extension on 3D-MDCT images was determined by detailed observation of volume-rendered images and multi-planar views of the tumor, measured in two rectangular directions. Observation of the tumor images by rotating and slicing them in multiple directions was found to be important to distinguish between cancerous and non-cancerous lesions. By studying the patients in the learning set, we could attain a good correlation of tumor size obtained from the 3D-MDCT images with pathologically determined tumor size ($r = 0.983$ for TS and $r = 0.958$ for VS). The subsequent validation study using the next 103 patients resulted in a very strong correlation between the two modalities for determining

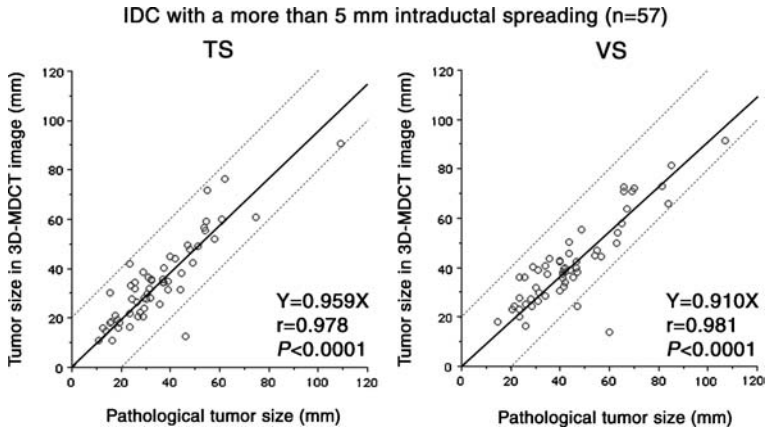

Figure 5. Relationship between tumor size obtained from 3D-MDCT images and pathologically determined tumor size for invasive ductal carcinomas with intraductal spreading of more than 5 mm ($n = 57$). Solid lines indicate regression coefficients and dotted lines indicate a 2 cm difference between the tumor sizes determined with the two modalities.

tumor size ($r = 0.974$ for TS and $r = 0.977$ for VS). Even when the analysis was limited to IDC tumors with an intraductal spread of more than 5 mm, the correlation was still very good ($r = 0.978$ for TS and $r = 0.981$ for VS).

Of the 103 tumors in the validation set, only five showed a more than 20 mm difference in tumor size between the 3D-MDCT image and pathological method. These results indicate that free surgical margins (≥5 mm) can be expected to be obtainable in more than 95% of patients if the breast gland is resected 1.5 cm outside the margin seen on the 3D-MDCT image. In addition, the analysis limited to IDC tumors with intraductal spreading of more than 5 mm ($n = 57$) showed that there was a difference of more than 20 mm in tumor size between the 3D-MDCT image and pathological determination in only two tumors. These results indicate that even in IDC tumors with intraductal spreading, which are generally considered difficult to visualize with conventional imaging modalities, free surgical margins (≥5 mm) can be expected to be obtainable in more than 96% of patients if the breast gland is resected 1.5 cm outside the margin seen on the 3D-MDCT image.

For DCIS tumors ($n = 10$), Pearson's correlation test also showed a strong correlation between 3D-MDCT and pathologically determined tumor size ($r = 0.948$ for TS and $r = 0.970$ for VS). However, the tumor border could not be determined accurately on the 3D-MDCT images of two DCIS tumors, which were fine intraductal lesions characterized by wide spreading in the breast gland accompanied by severe mastopathy. In these two tumors, the difference between the tumor size obtained from the 3D-MDCT image and the pathologically determined one was more than 20 mm. For ILC tumors ($n = 5$), a strong correlation was obtained between 3D-MDCT image and pathology determined tumor size ($r = 0.984$ for TS and $r = 0.976$ for VS) but one ILC tumor, with a difference of more than 20 mm between the sizes determined by the two modalities, could not be visualized on the 3D-MDCT image because of small multifocal lesions. These results for DCIS and ILC tumors, i.e., the difference between tumor sizes obtained from 3D-MDCT images and from pathological examination was less than 20 mm for 80% of DCIS (8/10) and 80% of ILC (4/5), indicate that the MDCT study appears to be promising for the preoperative evaluation of tumor extension in tumors which are generally considered to be very difficult visualize accurately with conventional imaging modalities.

To conclude, we have shown that 3D-MDCT images can be used to assess the tumor extension of breast cancer with a high degree of accuracy, and seems to be useful for planning the extent of resection in breast conserving surgery. Good cosmetic outcome combined with a low local recurrence rate can be expected to be achievable with the aid of 3D-MDCT imaging. To confirm the efficacy of 3D-MDCT, however, a study with a larger number of patients is needed.

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Address for offprints and correspondence: Shinzaburo Noguchi, MD Department of Surgical Oncology, Osaka University Graduate School of Medicine, 2-2-E10, Yamadaoka, Suita, Osaka 565-0871, Japan; *Tel.:* +81-6-6879-3772; *Fax:* +81-6-6879-3779; *E-mail:* noguchi@on-surg.med.osaka-u.ac.jp