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FULL PAPER

Intraoperative micro-computed tomography (micro-CT): a novel method for determination of primary tumour dimensions in breast cancer specimens

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Objectives: Micro-CT is a promising modality to determine breast tumour size in three dimensions in intact lumpectomy specimens. We compared the accuracy of tumour size measurements using specimen micro-CT with measurements using multimodality pre-operative imaging.

Methods: A tabletop micro-CT was used to image breast lumpectomy specimens. The largest tumour dimension on three-dimensional reconstructed micro-CT images of the specimen was compared with the measurements determined by pre-operative mammography, ultrasound and MRI. The largest dimension of pathologic invasive cancer size was used as the gold standard reference to assess the accuracy of imaging assessments.

Results: 50 invasive breast cancer specimens in 50 patients had micro-CT imaging. 42 were invasive ductal carcinoma, 6 were invasive lobular carcinoma and 2 were other invasive cancer. Median patient age was 63 years (range 33–82 years). When compared with the largest pathologic tumour dimension, micro-CT measurements had the best correlation coefficient ($r = 0.82$, $p < 0.001$) followed by MRI ($r = 0.78$, $p < 0.001$), ultrasound ($r = 0.61$, $p < 0.001$) and mammography ($r = 0.40$, $p < 0.01$). When compared with pre-operative modalities, micro-CT had the best correlation coefficient ($r = 0.86$, $p < 0.001$) with MRI, followed by ultrasound ($r = 0.60$, $p < 0.001$) and mammography ($r = 0.54$, $p < 0.001$). Overall, mammography and ultrasound tended to underestimate the largest tumour dimension, while MRI and micro-CT overestimated the largest tumour dimension more frequently.

Conclusion: Micro-CT is a potentially useful tool for accurate assessment of tumour dimensions within a lumpectomy specimen. Future studies need to be carried out to see if this technology could have a role in margin assessment.

Advances in knowledge: Micro-CT is a promising new technique which could potentially be used for rapid assessment of breast cancer dimensions in an intact lumpectomy specimen in order to guide surgical excision.

INTRODUCTION

While multiple pre-operative breast-imaging modalities are available for assessment of tumour size, each has its own limiting factors. Mammography is limited by variable radiographic appearances of tumours (calcifications, architectural distortion, asymmetry, mass etc.), faint tumour boundaries and failure of standard imaging to capture the maximum diameter.[1–4] In addition, dense breast tissue can make visualizing tumour margins difficult. Ultrasound, while more reliable than mammography, is limited by being operator and equipment dependent.[5–7] Some studies found that tumour size was significantly underestimated by ultrasound.[8,9] Contrast-enhanced MRI scans provide the most accurate image-based size measurement, but tend to overestimate tumour size.[8–11] Table 1 shows the correlation of tumour size measurement by pre-operative modalities with pathology.

Micro-CT is a new technology for breast tissue evaluation. It has a remarkable spatial resolution of 50-1 μm[22] and has been shown to be able to differentiate breast masses from fibrous breast tissue and differentiate benign calcifications

Table 1. Summary of studies with $n \geq 50$ reported correlation of tumour size measurement by pre-operative modalities and pathology

Study	Year	*n*	Correlation coefficient (*r*)		
			Mammography	Ultrasound	MRI
Luparia et al[12]	2013	149	0.83	0.77	0.92
Ramirez et al[13]	2012	277	0.76	0.67	0.75
Wasif et al[1]	2009	61	0.26	0.57	0.80
Onesti et al[14]	2008	71		0.47	0.65
Segara et al[6]	2007	68		0.61	0.75
Caramella et al[15]	2007	57	0.40	0.57	0.88
Shoma et al[16]	2006	124	0.42	0.66	
Bosch et al[17]	2003	96	0.44	0.68	
Kuroki et al[18]	2002	62			0.93
Partridge et al[10]	2002	52			0.89
Hieken et al[3]	2001	180	0.40	0.63	
Amano et al[19]	2000	58	0.63	0.55	0.78
Skaane[20]	1999	70	0.69	0.69	
Madjar et al[21]	1993	100	0.79	0.91	

from malignant ones.[23–26] It allows for three-dimensional (3D) evaluation of specimens up to 14 cm in size and can rapidly determine tumour dimensions. Micro-CT is self-shielded and compact enough to be placed near the operating room for convenient access.

In this study, we sought to determine if micro-CT could accurately measure invasive tumour size in breast lumpectomy specimens, and to evaluate the correlation of size measurement between micro-CT and pre-operative imaging.

METHODS AND MATERIALS

This study was approved by the Massachusetts General Hospital Institutional Review Board. Prospective written consent that allowed for additional imaging of excised breast tissue was obtained from patients undergoing lumpectomy for breast cancer from June 2011 to September 2011. Lumpectomy specimens from patients diagnosed with invasive cancer by pre-operative core biopsy were included in this study.

Once excised, lumpectomy specimens were placed in a plastic container and scanned using a tabletop Micro-CT, Skyscan® 1173 (Skyscan, Kontich, Belgium), with a 40–130 kV, 8W X-ray source. The scanner has <4–5 μm detail detectability and 7–8 μm low-contrast spatial resolution. Specimens were scanned at 40 kV, 200 mA, 500 ms exposure time and 360° of rotation. All scans were obtained between 0.4 and 0.8° of rotation, and one or two two-dimensional (2D) transmission images were obtained at each rotation step.

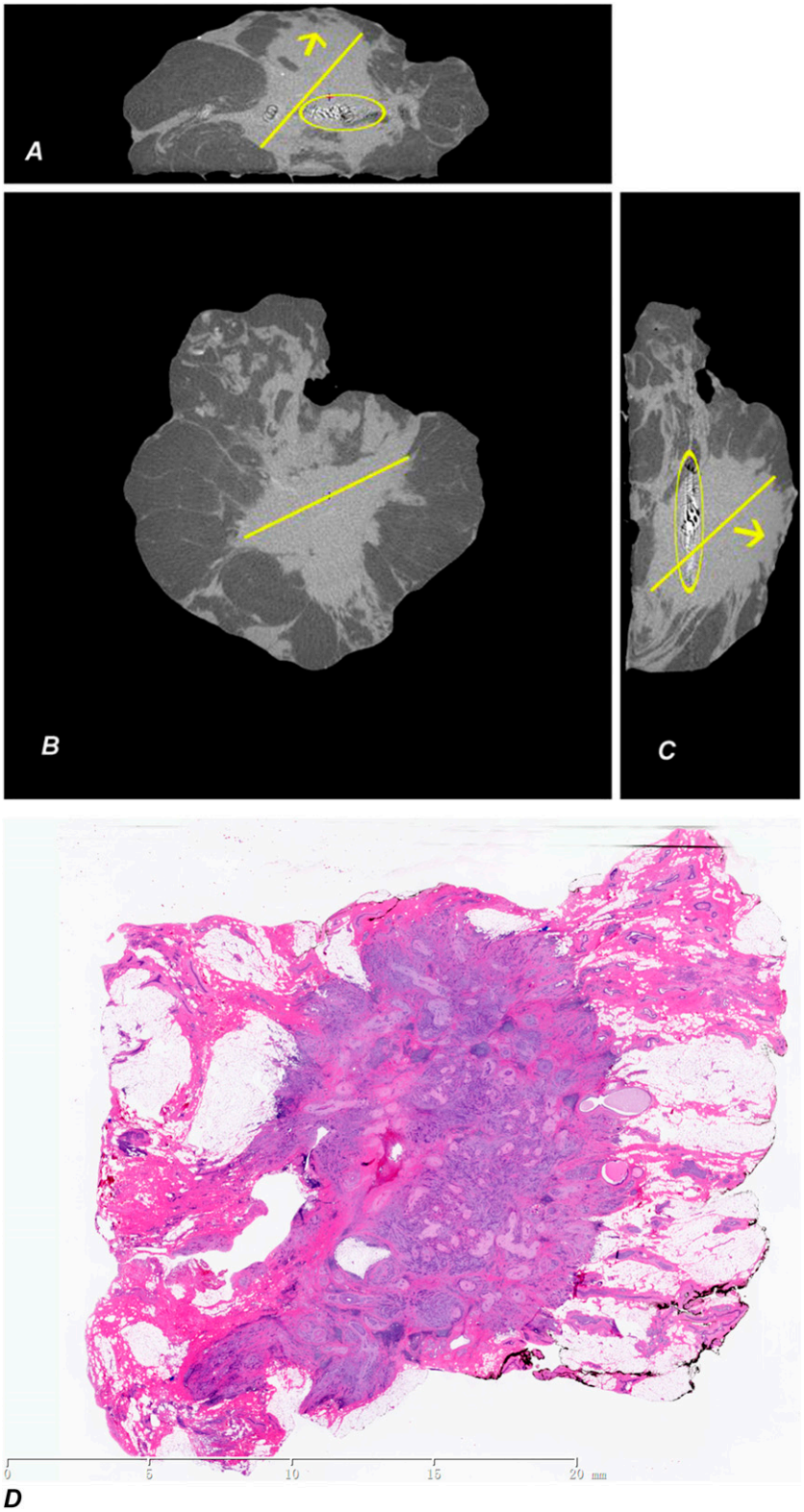
All 2D cross-sections were also fully reconstructed using Skyscan's NRecon program. Specimens scanned with an 0.8° rotation step with one 2D transmission image typically took 7 min to scan and an additional 7 min for 3D reconstruction. To review 3D graphics of the specimens, Skyscan software for 3D image analysis (DataViewer and CTVox) was employed.

In all modalities, tumour size was measured as the maximum tumour diameter. Ultrasound and MRI tumour sizes were retrospectively collected from written reports. Pre-operative mammograms were retrospectively reviewed by a dedicated breast radiologist (MS). Reconstructed micro-CT images underwent a blind evaluation by a trained physician to determine tumour size in three CT image planes (sagittal, transverse and coronal). (Figure 1a–c). For mammograms and micro-CT, only distinct mass lesions or distinct areas of abnormalities (such as density or architecture distortion) were measured as tumour, while calcifications alone were not included in size measurement. Mammogram and micro-CT evaluators were blinded to other imaging measurements and pathology results.

Surgical specimens were processed in the standard fashion.[27] Pathology assessment of the maximum diameter of invasive component of cancer was collected and used as the reference to determine the accuracy of imaging assessments. Pathology measurement is primarily obtained from a gross measurement on the excised specimen. In some cases, the gross measurement of the tumour size is modified after microscopic evaluation, which may show a smaller or larger tumour size (Figure 1d). Micro-CT, mammography and ultrasound tumour sizes were compared with pathology tumour size separately.

Correlations were assessed by Pearson's correlation coefficient for each of the imaging modalities. All data were analysed using SPSS analytical software.

Figure 1. Micro-CT image of a breast lumpectomy specimen with the largest dimension in three planes, (a) sagittal, (b) transverse and (c) coronal. The three planes can be shown simultaneously and evaluated separately. Arrow, a close margin (<0.1 cm) was confirmed by histopathology; circle, post-biopsy clip. (d) Histology: tumour: 2.1 × 1.6 × 1.2 cm invasive ductal carcinoma (IDC). Margin: IDC, ductal carcinoma *in situ* extends to <0.1 cm along a broad front.



RESULTS

50 patients with invasive breast malignancy were included in the study. The mean age was 63 years (range 33–82 years). The primary tumours were invasive ductal carcinoma (42), invasive lobular carcinoma (6) and invasive tubular cancer (2). Each patient had one lumpectomy specimen. Table 2 shows tumour characteristics.

All the 50 (100%) patients had had pre-operative mammography and intraoperative micro-CT; 42 (84%) patients had had ultrasound and 16 (32%) patients also had had pre-operative MRI.

On mammography, the primary tumour presented as a mass in 27 patients, architectural distortion/asymmetry in 10 patients, density in 3 patients, calcifications in 8 patients and was negative in 2 patients. In 40 of 50 (80%) mammograms, the size of the tumour or abnormality could be reliably measured.

Pathological assessment of the maximum diameter of the invasive component of the primary tumour was used as the reference to determine the accuracy of imaging assessments. In this cohort, the mean pathologic tumour size was 1.34 ± 0.63 cm. Mean tumour size by micro-CT, mammography and ultrasound was 1.42 ± 0.56 cm, 1.23 ± 0.80 cm and 1.25 ± 0.57 cm, respectively. Of the 16 patients who had had MRI, mean MRI tumour size was 1.66 ± 0.67 cm, and mean pathologic tumour size of this group was 1.52 ± 0.71 cm (Table 3).

Micro-CT had the highest accuracy, as the maximum tumour dimension by micro-CT was within 0.2 cm of the pathologic tumour size in 40 (80%) cases. Maximum tumour dimension was within 0.5 cm of pathologic tumour size in 44 (88%) micro-CT cases, 13 (81%) MRI cases, 33 (79%) ultrasound cases and 35 (70%) mammography cases. All modalities were relatively accurate at the 1 cm level; the accuracy of ultrasound, micro-CT, MRI and mammography at this level was 100%, 98%, 94% and 92%, respectively (Table 3).

Table 2. Characteristics of tumours

Characteristic	*n* (%)
Palpable mass	16 (32)
Post-menopausal	37 (74)
Tumour types	
IDC	8 (16)
IDC + focal DCIS	14 (28)
IDC + extensive DCIS	20 (40)
ILC	6 (12)
Others	2 (4)
Tumour size by AJCC staging	
T_1 (≤2 cm)	38 (76)
T_2 (>2 cm)	12 (24)

AJCC, American Joint Commitee on Cancer; DCIS, ductal carcinoma *in situ*; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma.

Comparative analysis demonstrated that of the four imaging techniques, mammography and ultrasound most frequently underestimated tumour size, while MRI and micro-CT tended to overestimate tumour size in this data set (Table 3). When compared with tumour size as determined by pathology assessment, micro-CT measurements had the best reflected pathology tumour size, indicated by the highest correlation coefficient ($r = 0.82$, $p < 0.001$), followed by MRI ($r = 0.78$, $p < 0.001$), ultrasound ($r = 0.61$, $p < 0.001$) and mammography ($r = 0.40$, $p = 0.004$) (Figure 2). When compared with pre-operative modalities, tumour size measured by intraoperative micro-CT correlated best with pre-operative MRI size ($r = 0.86$, $p < 0.001$), followed by ultrasound ($r = 0.60$, $p < 0.001$) and then mammography ($r = 0.54$, $p < 0.001$).

DISCUSSION

Breast conservation therapy is a well-established method of treating breast cancer. However, for effective treatment of breast cancer using breast conservation, it is imperative that the primary tumour be excised in its entirety. Micro-CT is a new imaging modality with a remarkable spatial resolution of 50-1 μm. While a prior study has shown the efficacy of chest CT in determining primary tumour size in breast cancer,[28] micro-CT had not been previously assessed for its accuracy in measuring primary tumour size. This study aimed to assess the accuracy of intraoperative micro-CT in measuring primary breast tumour size within lumpectomy specimens.

We assessed the tumour size on micro-CT because intraoperative use of micro-CT could impact surgery by comparing tumour dimension on micro-CT with pre-operative images, especially MRI (good dimension concordance with micro-CT, $r = 0.86$), to evaluate if the entire tumour is within the lumpectomy specimen. If the entire tumour is not within the lumpectomy specimen, then further surgery would be indicated. In addition, micro-CT can evaluate tumour dimensions in an intact specimen. This allows the physician to measure the tumour in 3D. Hence, it gives an advantage over the more traditional specimen radiograph, which allows evaluation only in 2D.

We found that among standard pre-operative imaging modalities, tumour size measured by MRI had the highest correlation with histopathological invasive tumour size, followed by ultrasound and mammography. This finding is consistent with prior studies (Table 1).[1,3,6,12–21]

Tumour size measured by micro-CT correlated better with histopathological invasive tumour size than any of the three pre-operative imaging modalities. This is likely because micro-CT generates higher resolution images, making fine structures, anatomic features and tumour boundaries more clearly visible. Also, micro-CT is able to create multiplanar, cross-sectional images of the internal structure of intact

Table 3. Comparing size assessed by micro-CT, mammography, ultrasound and MRI

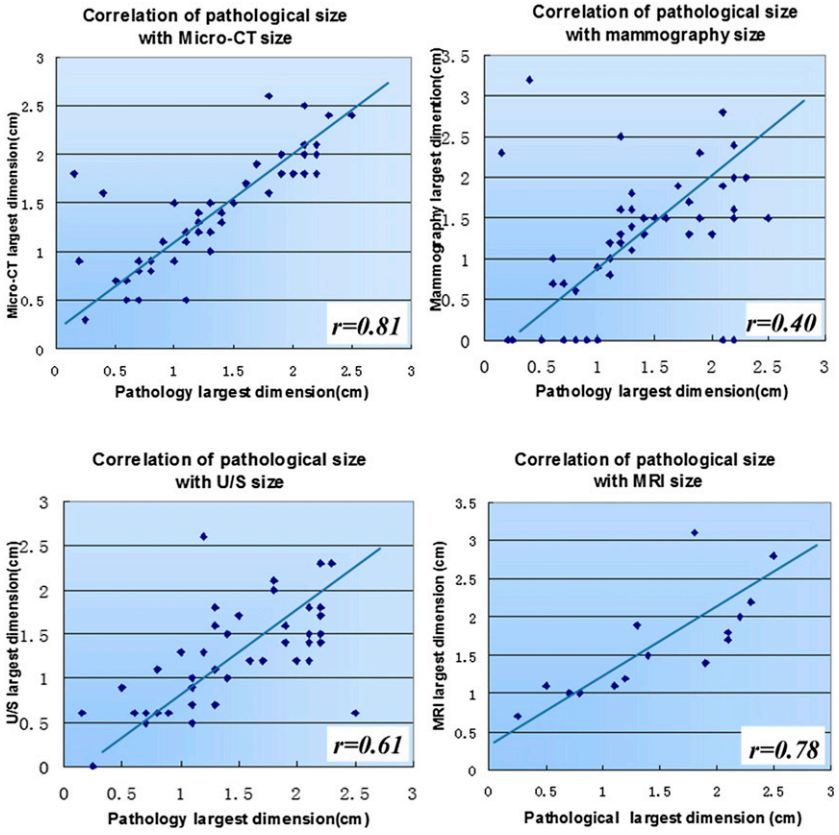
Property studied	Pathology	Micro-CT	Mammography	Ultrasound	MRI
Studied cases (%)	50 (100)	50 (100)	50 (100)	42 (84)	16 (32)
Tumour size (cm) (mean ± SD)	1.34 ± 0.63	1.42 ± 0.56	1.23 ± 0.80	1.25 ± 0.57	1.66 ± 0.67
Tumour size measurement					
Measured larger than pathology (%)	/	23 (46)	18 (36)	14 (33)	8 (50)
Measured smaller than pathology (%)	/	18 (36)	28 (56)	26 (62)	6 (38)
Accuracy					
Accurate within 0.2 cm of pathology (%)	/	40 (80)	24 (48)	14 (33)	7 (44)
Accurate within 0.5 cm of pathology (%)	/	44 (88)	35 (70)	33 (79)	13 (81)
Accurate within 1 cm of pathology (%)	/	49 (98)	46 (92)	42 (100)	15 (94)
Correlation coefficient					
Pathology (r)	/	0.81	0.40	0.61	0.78
Micro-CT (r)	/	/	0.54	0.60	0.86

SD, standard deviation.

specimens, allowing for evaluation of tumour size in all directions. Furthermore, micro-CT tumour size correlated well with pre-operative MRI tumour size ($r = 0.86$). This finding suggests that intraoperative micro-CT tumour size measurement could be a promising method to determine adequate removal of invasive breast cancers.

A limitation of this study is that MRI was performed in only one-third of cases. This is because our practice is to use pre-operative MRI selectively in new patients with breast cancer. Although our correlation of MRI is consistent with prior studies, the small case number could influence the accuracy of comparison of MRI with micro-CT.

Figure 2. Correlation between pathologic tumour size and imaging tumour size assessed by micro-CT, mammography, ultrasound (U/S) and MRI.



In addition, there were some difficulties in measuring the tumour size with micro-CT: similar to mammography, micro-CT identifies tumour mainly through tissue greyscale differences and morphology; thus, some fibroglandular tissue or fibrous tissue might be mistakenly identified as tumour and cause overestimation of tumour size. It was also challenging to determine the border of the primary invasive tumour in some cases when the invasive component was surrounded by extensive ductal carcinoma in situ with microcalcifications. In addition, the tendency of micro-CT to overestimate the tumour size compared with histopathological measurement is likely secondary to the fact that micro-CT evaluates in 3D. We recorded the largest dimension which might be missed in the 2D measurements performed on histology.

Micro-CT images underwent blinded evaluation by a trained physician to determine tumour size. Additional studies are planned to develop a training and testing system to improve and standardize the performance of individuals reading micro-CT images and to assess reproducibility in more general use.

Another drawback of micro-CT is the time it takes to gather and reconstruct images. The average 14 min required to obtain images for review may be too long for some lumpectomy procedures. It may be possible, however, to reduce the impact of scanning time through modifications in surgical workflow. For example, if lumpectomy is the first step in the surgical procedure, micro-CT scanning could be performed while the surgeon performs sentinel lymph node biopsy or axillary dissection. Moreover, model reconstruction time in this study (median 7 min) was obtained with a basic office PC and could be reduced dramatically with optimized hardware. Improvements in micro-CT technology may ultimately allow for more rapid image acquisition and may come closer to the goal of accurate, real-time lumpectomy specimen assessment.

In conclusion, micro-CT is a promising new technique which could potentially be used for rapid intraoperative assessment of breast cancer dimensions within a lumpectomy specimen in order to guide surgical excision. Furthermore, studies are warranted to assess its impact on other factors such as margin assessment and re-excision rates.

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