Original Article

Prediction of primary breast cancer size and T-stage using micro-computed tomography in lumpectomy specimens

Wafa M. Sarraj[1], Rong Tang[1,2], Anas L. Najjar[1], Molly Griffin[1], Anthony H. Bui[1], Alan Zambeli-Ljepovic[1], Mike Senter-Zapata[1], Maya Lewin-Berlin[1], Leopoldo Fernandez[1], Juliette Buckley[1], Amy Ly[3], Elena Brachtel[3], Owen Aftreth[1], John Gilbertson[3], Yukako Yagi[3], Michele Gadd[1], Kevin S. Hughes[1], Barbara L. Smith[1], James S. Michaelson[1,3]

[1]Division of Surgical Oncology, Gillette Center for Women's Cancers, Massachusetts General Hospital, [3]Department of Pathology, Massachusetts General Hospital, Boston, MA 02114, USA, [2]Division of Breast Surgery, Hunan Cancer Hospital, The Affiliated Cancer Hospital of Xiangya Medical School of Central South University, Changsha 410013, China

E-mail: *Dr. Wafa M. Sarraj – wmsarraj@gmail.com
*Corresponding author

Abstract

Background: Histopathology is the only accepted method to measure and stage the breast tumor size. However, there is a need to find another method to measure and stage the tumor size when the pathological assessment is not available. Micro-computed tomography (micro-CT) has the ability to measure tumor in three dimensions in an intact lumpectomy specimen. In this study, we aimed to determine the accuracy of micro-CT to measure and stage the primary tumor size in breast lumpectomy specimens, as compared to the histopathology. **Materials and Methods:** Seventy-two women who underwent lumpectomy surgery at the Massachusetts General Hospital Department of Surgery from June 2011 to September 2011, and from August 2013 to December 2013 participated in this study. The lumpectomy specimens were scanned using micro-CT followed by routine pathological processing. The maximum dimension of the invasive breast tumor was obtained from the micro-CT image and was compared to the corresponding pathology report for each subject. **Results:** The invasive tumor size measurement by micro-CT was underestimated in 24 cases (33%), overestimated in 37 cases (51%), and matched it exactly in 11 cases (15%) compared to the histopathology measurement for all the cases. However, micro-CT T-stage classification differed from histopathology in only 11 (15.2%) with 6 cases (8.3%) classified as a higher stage by micro-CT, and 5 cases (6.9%) classified as lower compared to histopathology. In addition, micro-CT demonstrated a statically significant strong agreement (κ =0.6, P < 0.05) with pathological tumor size and staging for invasive ductal carcinoma (IDC) group. In contrast, there was no agreement (κ = $-$2, P = 0.67) between micro-CT and pathology in estimating and staging tumor size for invasive lobular carcinoma (ILC) group. This could be explained by a small sample size (7) for ILC group. **Conclusions:** Micro-CT is a promising modality for measuring and staging the IDC.

Key words: Breast cancer, breast imaging, gross pathology, micro-computed tomography, tumor size

INTRODUCTION

Tumor size is a major determinant for staging and predicting the outcome for cancer patients.[1] According to the American Joint Committee on Cancer TNM staging system for breast cancer, the invasive primary tumor size classifies the breast cancer pathologically into five groups. T0 for tumors that are undetectable grossly, T1 for tumors measured ≤2 cm, T2 for tumors measured >2 cm –5 cm, T3 for those measured >5 cm, and T4 for tumors of any size with infiltration either to the skin or chest wall.[2] Because of this staging system, it is important to report an accurate measurement of primary tumor size since 1 mm variation in the measurement can lead to a change in T-stage classification, which in turn will alter the patient's treatment options.[3]

Although the pathology is the gold standard for measuring and staging the tumor size, there are certain factors that could affect the accuracy of tumor measurement. [3] These include fixation of the tissue in the formalin, which might cause tissue expansion or shrinkage, as well as the histological type and growth pattern of the tumor.[3] For example, invasive ductal carcinoma (IDC), which is the most common type of breast cancer, can be measured easily during gross examination because it forms a mass that has circumscribed irregular borders. On the other hand, invasive lobular carcinoma (ILC), which accounts for only 5–10% of all breast cancers, tends to grow in a diffuse pattern, without forming a mass.[4] Because of this, measuring and staging the ILC grossly is challenging. Another situation that could potentially comprise the measurement and staging of the tumor occurs when the pathological assessment is not available, or cannot be performed due to shortage of laboratory materials. To deal with this, breast imaging modalities such as breast ultrasound, mammography, and magnetic resonance imaging are used to stage the tumor clinically and inform treatment options for the patients.[5] However, previous studies have shown none of these modalities are accepted as the standard for tumor size measurement.[6-14]

Micro-computed tomography (micro-CT) is a noninvasive X-ray technology that provides high-resolution (10 μm) three-dimensional (3D) images of *ex vivo* specimens.[15] With this method, it is possible to visualize and obtain the 3D measurements of the invasive tumor without cutting the tumor, as is the case in the pathological procedure. Few studies have used micro-CT technology to evaluate the interior structure of breast tissue.[16,17] These studies demonstrated that micro-CT is capable of identifying the different components of breast tissue, as well as differentiating between benign and malignant breast tumor. However, none of these studies measured the malignant tumor size because they were performed on breast core biopsy specimens, which contain only a small section of the lesion and may not be representative of a breast lesion. Since none of the modalities that described above were shown to perform adequate tumor measurement, a new modality is needed. micro-CT may help to confirm the final pathological tumor size measurement in cases where the invasive tumor size could be larger or smaller than gross examination would demonstrate. Therefore, micro-CT can serve as a clinical decision support system for measurement and staging of invasive breast cancers.

The first objective of this study was to evaluate the accuracy of micro-CT in measuring the tumor size in breast lumpectomy specimens and to determine whether there is a change in T-stage when the micro-CT tumor size was different from the pathological tumor size in both invasive ductal and lobular carcinoma. The second objective was to assess the sensitivity and specificity of micro-CT in detecting the malignant tumor size ≤2 cm.

MATERIALS AND METHODS

This study was approved by the Massachusetts General Hospital (MGH) institutional review board. The study was conducted in two periods, the first period was from June 2011 to September 2011, and the second period was from August 2013 to December 2013. Specimens from women with a confirmed diagnosis of breast cancer by biopsy, and who were scheduled to have breast lumpectomy surgery for the first time during the aforementioned periods were scanned. Only those who were diagnosed with invasive breast cancer were included in this study. Those who were diagnosed with noninvasive breast disease such as benign lesions, or *in situ* disease and those who were scheduled to have breast re-excision surgery were excluded from the study. All the participants were consented prior to their participation in the study before or on the day of the surgery.

Micro-Computed Tomography Measurements

Once the malignant tumors were excised from the patients, they were scanned by one of two machines: A tabletop micro-CT SkyScan 1173 (Bruker Corporation, SkyScan, Belgium), which was used to scan the first 50 invasive cancer specimens, or a micro-CT Nikon XT H 225 system (Nikon, Japan) which scanned the rest of the specimens. Both machines were calibrated in the early morning on the day of the surgery. In addition, the both machines have the similar structural and functional proprieties. They are composed of an X-ray microfocus tube that has a voltage range of 40–130 kV, and power of 8 W as X-ray sources, a rotatory movable stage, and a detector. Each specimen was placed inside a transparent container before being placed on the rotary stage, where it was rotated 360° and scanned at 0.40–0.80° incremental rotation steps. Each scan lasted no longer than 15 min. Some specimens had a localized needle wire, which was removed gently before scanning

the specimens to avoid the image artifacts. The excised specimens were delivered to the pathology grossing laboratory after the scan was completed, where they were processed via the standard pathological protocol.

Dedicated micro-CT technicians assembled a 3D image representation of the specimen from the raw scan data using SkyScan's NRecon and VideoGraphics Laboratory (VGL) studio programs. The reconstructed images were analyzed using the following software: Data viewer, CTVox, and VGL studio [Figure 1].

The images were previewed from three orthogonal perspectives: From the X-rays source, from the micro-CT window on the right side, and from the top down. Before the linear measurement was obtained, the measurement tool was calibrated by centimeters.

The micro-CT measurements were performed by an independent physician who was blinded to the pathology results and the medical records. The physician was also trained to read the micro-CT images. The single linear measurement of the largest diameter of the tumor was recorded after identifying the tumor edges in the micro-CT image.

Pathological Measurements

The specimens were processed following routine pathology procedures by the pathologist or pathologist assistant. The excised specimens were inked on the surface with one color if the surgeon provided no further orientation. If the specimens were oriented, an inking protocol with four colors was used in the gross examination. The specimens were serially sectioned
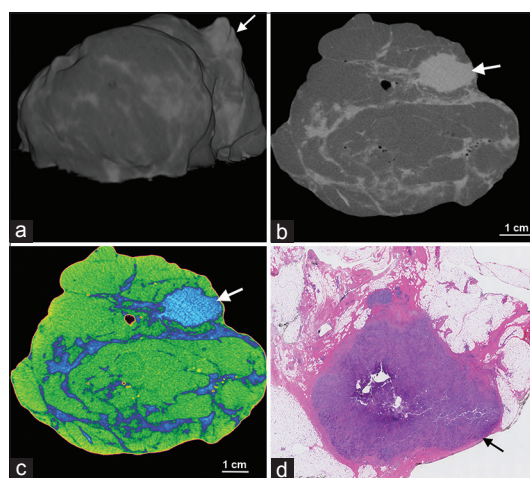

Figure 1: (a) A three-dimensional micro-computed tomography image of a lumpectomy specimen shows a part of the tumor mass (arrow); (b) a cross-sectional image shows the whole tumor mass (arrow); (c) the recorded micro-computed tomography maximum dimension of the tumor is 1.2 cm, found with a special contrast agent used to visualize the tumor edges clearly before taking the measurement; (d) a histopathology of the same case (c) invasive ductal carcinoma Grade 3, with maximum dimension of 1.2 cm. This measurement is consisting with micro-computed tomography measurement

in a fresh state, and the gross examination findings were recorded as a part of the routine pathology report, which included size and characteristics of the grossly recognized mass, distance to the inked margins, and findings in the surrounding breast parenchyma. Additional findings such as needle orientation wires or radiographic clips were also recorded. In most cases, representative sections of the tumor with closest margins were formalin-fixed and paraffin-embedded by routine histopathological processing procedures. In some cases without grossly recognizable masses, the breast excision specimen was entirely submitted. 5 um sections were cut and stained with Hematoxylin and Eosin, and microscopically evaluated by the pathologist.[2,18,19] Tumor size measurements were based on either the gross or microscopic examinations or a combination of these. The cases were evaluated and reported by breast pathologists. Information from the pathology reports was subsequently extracted for this study.

Statistical Data Analysis

For descriptive analysis of the sample features, mean, standard deviation (SD), and percentage were calculated.

For the outcome measures, the percentages of the micro-CT cases that yielded a larger, smaller, or equal size compare to the pathology report were calculated. The match cases were defined as the micro-CT tumor size cases that matched to the pathological tumor size cases to the first decimal place. In addition, the percentage of changes in T-stage was assessed when micro-CT tumor size measurement was different from the pathology.

The study subjects were categorized into two groups based on invasive tumor maximum dimension in the TNM classification staging system. Group 1 contained subjects with tumor maximum dimension ≤2 cm, which is referred to as stage T1. Group 2 contained subjects with tumor maximum dimension >2 cm, which is referred to as stage T2.

Validity measurements such as sensitivity and specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated with 95% confidence intervals (CIs). Group 1 with tumor size ≤2 cm was treated as the positive result. The reason behind this was to evaluate the ability of micro-CT to detect the tumor size with the maximum dimension of ≤2 cm in across.

Cohen's Kappa was calculated with 95% CIs to measure the agreement between micro-CT and pathology. To assess the agreement graphically between the micro-CT and pathology in measuring the maximum dimension of the invasive tumor, an Altman-Bland plot with 95% limit of agreement was generated.

$P \leq 0.05$ were considered statistically significant. All the study analyses were carried out using R version 3.0.3.[20]

RESULTS

72 female subjects who were diagnosed with primary invasive breast cancer and subsequently underwent breast lumpectomy were examined in detail in this study. Among 72 lesions, 65 cases (90.3%) were IDC, and 7 cases (9.7%) were ILC. 8 out of 65 cases (12%) of IDC did not have *in situ* disease. The final diagnosis of ILC cases was confirmed by having negative E-cadherin stain [Table 1].

The mean diameter and SD via micro-CT measurement was 1.40 cm (±0.73), with measurement was ranging

from 0.2 to 3.8 cm, while the mean diameter and SD by pathological measurement was 1.36 cm (±0.73), with measurement was ranging from 0.15 to 3.5 cm for IDC. For the ILC, the mean diameter and SD via micro-CT measurement was 1.90 cm, with measurement was ranging from 1.1 to 2.9 cm, while the mean diameter and SD by pathological measurement was 1.35 cm, with measurement was ranging from 0.25 to 2.1 cm.

Table 2 shows that the micro-CT measurement yielded a slightly smaller size than pathology tumor size measurement in 32% of cases, yielded a larger size in 51% of cases, and an equivalent size in 17% of cases for IDC. For the ILC, the micro-CT measurement yielded a slightly smaller size than the pathology tumor size measurement in 43% of cases, yielded a larger size in 57% of cases, and equivalence in none of the cases. Overall, micro-CT measurement yielded a slightly smaller size than pathology tumor size measurement in 24 cases (33%), yielded a larger size in 37 cases (51%), and an equivalent size in 11 cases (15%) for all breast cancer cases.

Table 3 shows that micro-CT T-stage classification of IDC differed from pathology classification in 12.3% of cases, with micro-CT classifying 7.7% of cases in a higher stage than pathology and 4.6% of cases in a lower stage. However, micro-CT and pathology classification were no different in 88% of cases. For ILC group, micro-CT and pathology T-stage classification were different in 43% of cases, with micro-CT classifying 14% of cases in a higher stage than pathology and 29% of cases in a lower stage. Generally, micro-CT and pathology T-stage classification were different only in 11 out of 72 cases (15.2%) in total, with micro-CT classifying 6 cases (8.3%) higher than pathology and 5 cases (6.9%) lower than pathology for all breast cancer cases.

For the validity measurements, 50 IDC tumors were measured ≤2 cm by pathology, and 52 IDC tumors

Table 1: Study sample features

Features	Case (*n*=72)
Demographics	
Age, year±SD	64.08±13.27
Age, *n* (%)	
30-39	2 (2.8)
40-49	10 (14)
50-59	15 (21)
60-69	19 (26)
70-79	16 (22)
80-89	9 (12)
90-99	1 (1.4)
Menopausal status, *n* (%)	
Premenopausal	11 (15)
Postmenopausal	61 (85)
Type of cancer, *n* (%)	
IDC	65 (90.3)
ILC	7 (9.7)
Grade of IDC, *n* (%)	
Grade 1	11 (15)
Grade 2	46 (64)
Grade 3	15 (21)
Grade of ILC, *n* (%)	
Grade 2	7 (100)
Type of *in situ* component within the cancer, *n* (%)	
DCIS	
IDC	41 (63)
ILC	0 (0)
LCIS	
IDC	3 (4.6)
ILC	6 (86)
Both DCIS and LCIS	
IDC	13 (20)
ILC	1 (14)
Other findings in the breast cancer, *n* (%)	
Healing tissue	68 (94)
Benign lesion	40 (56)
Pathological T-stage, *n* (%)	
T1	56 (78)
T2	16 (22)

Percentages are based on the total number of each group, all percentages were rounded to 2 digits. DCIS: Ductal carcinoma *in situ* only, LCIS: Lobular carcinoma *in situ* only, IDC: Invasive ductal carcinoma, ILC: Invasive lobular carcinoma, SD: Standard deviation

Table 2: Comparison of tumor size measurement between Micro-CT and pathology

Group	Underestimate (%)	Overestimate (%)	Match (%)
IDC	21 (32)	33 (51)	11 (17)
ILC	3 (43)	4 (57)	0

Percentages are based on the total number of each group, all percentages were rounded to 2 digits, the match cases were defined as the micro-CT tumor size cases that matched to the pathological tumor size cases at the first decimal place. Micro-CT: Micro-computed tomography, IDC: Invasive ductal carcinoma, ILC: Invasive lobular carcinoma

Table 3: Comparison of T-stage classification between Micro-CT and pathology

Group	No change (%)	Changed (%)	Higher (%)	Lower (%)
IDC	57 (88)	8 (12.3)	5 (7.7)	3 (4.6)
ILC	4 (57)	3 (43)	1 (14)	2 (29)

The percentage based on the total number of the subjects on each group. Micro-CT: Micro-computed tomography, IDC: Invasive ductal carcinoma, ILC: Invasive lobular carcinoma

were measured ≤2 cm by micro-CT, corresponding to a sensitivity of 94% (95% CI: 0.83–0.99), a specificity of 67% (95% CI: 0.38–0.88), a PPV of 90% (95% CI: 0.79–0.97), and a NPV of 77% (95% CI: 0.46–0.95). For ILC, there were six tumors were measured ≤2 cm by pathology, while the micro-CT measured five tumors ≤2 cm, corresponding to a sensitivity of 67% (95% CI: 0.22–0.96), a specificity of 0%, a PPV of 80% (95% CI: 0.28–0.99), and an NPV of 0%.

Table 4 shows that the Kappa statistic demonstrated statistically significant agreement between the micro-CT and pathology for tumor size measurement and T-stage classification for IDC (κ =0.6) and no agreement for ILC (κ = −0.2) However, ILC agreement result was not statistically significant.

The Altman bland plots in [Figures 2 and 3] showed that the 95% limit of agreement between micro-CT and pathology measurements was –0.8 to 1 cm for IDC, and −1.6 to 2.9 cm for ILC. The solid line represents the mean difference between the two measurements, and the dashed line represents the upper and lower 95% limit of agreement.

DISCUSSION

In this study, we examined the agreement between micro-CT and pathology measurements of the breast

malignant tumor size in 72 subjects who had a confirmed diagnosis of primary breast cancer by histopathology.[21,22] To our best knowledge, we are the first to report the use of micro-CT in assessing the breast malignant tumor size of lumpectomy specimens. Our study demonstrated that micro-CT yields a slightly larger size than the pathological invasive tumor size in 37 cases out of 72 cases (51%). We would assume that the T-stage of the overestimated cases by micro-CT would be changed into lower stage after comparing to pathology. However, we found that T-stage changed into lower stage only in 5 out of 11 (6.9%) cases in which micro-CT and pathology yielded a different T-stage classification. In addition, a similar result was observed in 24 cases (33%) that were underestimated by the micro-CT, where only 6 cases out of 11 (8.3%) changed into a higher stage. This could be explained by our finding that the difference between the micro-CT and the pathology measurements were within the value range of each stage, which could be considered as a clinically insignificant.

The over/underestimation of invasive tumor size by micro-CT could be explained by tissue fixation in formalin and tissue processing. These factors could change the microscopic tumor size measurement by causing tissue expansion and shrinkage.[3] These effects can occur at any stages of the specimen processing from receiving the specimen in fixative solution to embedding the tissue in the paraffin blocks. One study reported a reduction of the tumor size measurement between the fresh specimens and the final processed specimens in 40% of 50 breast cancer cases, with a mean difference of 2.4 mm from the fresh specimen measurement, and increased of measured tumor size in 18% of the 50 cases with a mean difference of 1.7 mm.[23] In our study, we were unable to eliminate this effect completely in 15 cases where the tumor size was measured only by

Table 4: Kappa statistics for invasive tumor size and stage group in IDC, and ILC

Groups	Kappa coefficient (95% CI)	P
IDC	0.6 (0.402-0.873)	<0.05
ILC	−0.2 (−1.291-0.821)	0.675

IDC: Invasive ductal carcinoma, ILC: Invasive lobular carcinoma, CI: Confidence interval
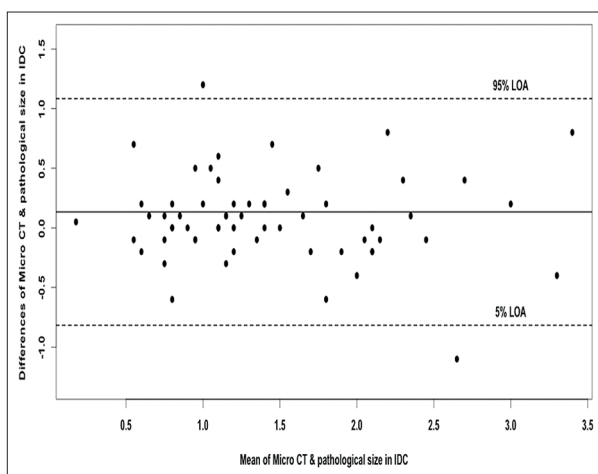

Figure 2: Bland-Altman plot illustrating the size difference between the micro-computed tomography and pathology against the size average of micro-computed tomography and pathology for invasive ductal carcinoma group
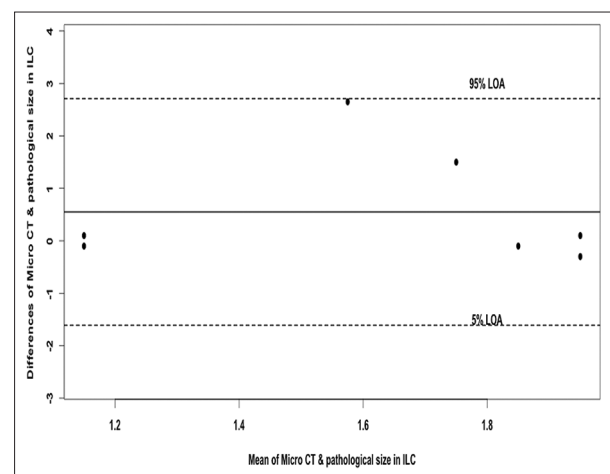

Figure 3: Bland-Altman plots illustrating the size difference between the micro-computed tomography and pathology against the size average of micro-computed tomography and pathology for invasive lobular carcinoma group

the microscope. However, for the rest of the cases, all the specimens were cut in the fresh state and measured during gross examination.

Additional explanations for the overestimation of tumor size could be due to other factors related to the lumpectomy procedure. The procedure can cause local bleeding and edema. Moreover, a previous core biopsy may cause an inflammatory reaction and fibrosis that could result in tumor size overestimation by micro-CT.[24,25]

This study also demonstrated a statistically significant substantial agreement for measuring and staging IDC tumors. However, there was no agreement for measuring and staging ILC tumors. Moreover, the ILC tumors exhibited the lowest sensitivity (67%), and no specificity, in detecting tumors ≤2 cm. These observations could be explained by the growth nature of ILC, which has a diffuse, less circumscribed growth pattern without forming any fibrosis, thus complicating identification of ILC margins in the images.[3,26] Hence, the micro-CT measured IDC more accurately than ILC. Further, the small number of ILC cases in the study compared to IDC cases may explain the lack of agreement between micro-CT and pathology measurements of ILC tumor size.

This study had limitations. The first limitation is the small sample size. Since this technology is not a part of standard care, few subjects were enrolled in this study. Additional assessment of micro-CT using a large sample size is required to validate micro-CT tumor size measurement. Moreover, further research is required to assess the agreement between micro-CT and pathology measurements for ILC group.

The second limitation is that the study results can only be generalized to postmenopausal women with an early stage of breast cancer who were treated at the MGH. Because of this, great caution should be considered when interpreting these findings to the general population.

Third, although the definitive tumor size is usually obtained by pathologic measurement, the possibility of variation in tumor size measurement by pathology cannot be excluded because different pathologists performed the tumor size measurement in our study, which could affect the internal validity of these measurements. However, a previous study that was conducted by NHS breast cancer screening program to assess the performance of pathologists by circulating standardized breast cancer slides found that >90% agreement between pathologists in measuring tumor size.[27]

Finally, because of the small sample size, we were unable to evaluate the effect of the breast cancer grade and presence and percentage of carcinoma *in situ* components (ductal carcinoma *in situ* and lobular carcinoma in situ) in measuring and staging tumor size. These factors could have contributed to errors in micro-CT measurement toward the overestimation of tumor size using micro-CT measurement.

Even with these limitations, this study had strengths. First, the micro-CT measurements were performed by an independent physician who received appropriate training in reading the micro-CT images and measuring the tumor size. In addition, the physician was blinded to the pathology reports and medical records of the subjects. The micro-CT machine was also calibrated before scanning each lumpectomy specimen, limiting a measurement bias.

Second, because this was a pilot study, it will help to determine the appropriate sample size to assess the micro-CT breast tumor measurement for a larger study, in order to obtain meaningful results. Moreover, we were able to identify the study limitations that can be addressed in the larger study.

CONCLUSIONS

In our small study, although the micro-CT tends to yield a slightly larger measurement of breast malignant tumor than the pathological measurement, micro-CT shows statistically significant strong agreement with histopathological examination in measuring and staging the breast malignant tumors for IDCs. No agreement was found between micro-CT and pathological measurement for ILC. Further investigation is required to evaluate the micro-CT in measuring the ILC.

Financial Support and Sponsorship

Conflicts of Interest
There are no conflicts of interest.

REFERENCES

1. Michaelson JS, Silverstein M, Wyatt J, Weber G, Moore R, Halpern E, *et al.* Predicting the survival of patients with breast carcinoma using tumor size. Cancer 2002;95:713-23.
2. American Joint Committee on Cancer. AJCC Cancer Staging Manual. 6th ed. New York, PA: Springer; 2002. p. 227-8.
3. Pritt B, Weaver DL. Accurate determination of breast cancer size: The role of histopathology and imaging. Curr Diagn Pathol 2005;11:435-42.
4. Lester S, Montag A. Female Genital System and breast. In: Kumar V, Abbas AK, Aster C, editors. Robbins Basic Pathology. 9th ed. Philadelphia, PA: Elsevier Saunders; 2013. p. 710-2.
5. Lester SC, Bose S, Chen YY, Connolly JL, de Baca ME, Fitzgibbons PL, *et al.* Protocol for the examination of specimens from patients with invasive carcinoma of the breast. Arch Pathol Lab Med 2009;133:1515-38.
6. Pierie JP, Perre CI, Levert LM, de Hooge P. Clinical assessment, mammography and ultrasonography as methods of measuring the size of breast cancer: A comparison. Breast 1998;7:247-50.
7. Finlayson CA, MacDermott TA. Ultrasound can estimate the pathologic size of infiltrating ductal carcinoma. Arch Surg 2000;135:158-9.
8. Skaane P, Skjørten F. Ultrasonographic evaluation of invasive lobular carcinoma. Acta Radiol 1999;40:369-75.

9. Yang WT, Lam WW, Cheung H, Suen M, King WW, Metreweli C. Sonographic, magnetic resonance imaging, and mammographic assessments of preoperative size of breast cancer. J Ultrasound Med 1997;16:791-7.

10. Flanagan FL, McDermott MB, Barton PT, Pilgram TK, Dehdashti F, Wick MR, *et al.* Invasive breast cancer: Mammographic measurement. Radiology 1996;199:819-23.

11. Hieken TJ, Harrison J, Herreros J, Velasco JM. Correlating sonography, mammography, and pathology in the assessment of breast cancer size. Am J Surg 2001;182:351-4.

12. Bosch AM, Kessels AG, Beets GL, Rupa JD, Koster D, van Engelshoven JM, *et al.* Preoperative estimation of the pathological breast tumour size by physical examination, mammography and ultrasound: A prospective study on 105 invasive tumours. Eur J Radiol 2003;48:285-92.

13. Golshan M, Fung BB, Wiley E, Wolfman J, Rademaker A, Morrow M. Prediction of breast cancer size by ultrasound, mammography and core biopsy. Breast 2004;13:265-71.

14. Dummin LJ, Cox M, Plant L. Prediction of breast tumor size by mammography and sonography – A breast screen experience. Breast 2007;16:38-46.

15. Ritman EL. Current status of developments and applications of micro-CT. Annu Rev Biomed Eng 2011;13:531-52.

16. Gufler H, Franke FE, Wagner S, Rau WS. Fine structure of breast tissue on micro computed tomography a feasibility study. Acad Radiol 2011;18:230-4.

17. Gufler H, Wagner S, Franke FE. The interior structure of breast microcalcifications assessed with micro computed tomography. Acta Radiol 2011;52:592-6.

18. Tavassoli FA, Devilee P, editors. World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Breast and Female Genital Organs. Lyon: IARC Press; 2003.

19. Rosen P. Rosen's Breast Pathology. 3th ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2009.

20. R Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2012. Available from: http://www.R-project.org/. [Last accessed on 2015 Jun 15].

21. Tang R, Buckley JM, Fernandez L, Coopey S, Aftreth O, Michaelson J, *et al.* Micro-computed tomography (Micro-CT): A novel approach for intraoperative breast cancer specimen imaging. Breast Cancer Res Treat 2013;139:311-6.

22. Tang R, Coopey SB, Buckley JM, Aftreth OP, Fernandez LJ, Brachtel EF, *et al.* A pilot study evaluating shaved cavity margins with micro-computed tomography: A novel method for predicting lumpectomy margin status intraoperatively. Breast J 2013;19:485-9.

23. Pritt B, Tessitore JJ, Weaver DL, Blaszyk H. The effect of tissue fixation and processing on breast cancer size. Hum Pathol 2005;36:756-60.

24. Gann PH, Colilla SA, Gapstur SM, Winchester DJ, Winchester DP. Factors associated with axillary lymph node metastasis from breast carcinoma: Descriptive and predictive analyses. Cancer 1999;86:1511-9.

25. Pain JA, Ebbs SR, Hern RP, Lowe S, Bradbeer JW. Assessment of breast cancer size: A comparison of methods. Eur J Surg Oncol 1992;18:44-8.

26. Moatamed NA, Apple SK. Extensive sampling changes T-staging of infiltrating lobular carcinoma of breast: A comparative study of gross versus microscopic tumor sizes. Breast J 2006;12:511-7.

27. National Coordinating Group for Breast Screening Pathology. Pathology Reporting in breast screening pathology. 2nd ed. Sheffield, UK: NHSBSP Publications; 1997.