

Micro-computed tomography (Micro-CT): a novel approach for intraoperative breast cancer specimen imaging

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Abstract Intraoperative radiographic examination of breast specimens is commonly performed to confirm excision of image-detected breast lesions, but it is not reliable for assessing margin status. A more accurate method of intraoperative breast specimen imaging is needed. Micro-CT provides quantitative imaging parameters, image rotation, and virtual “slicing” of intact breast specimens. We explored the use of micro-CT for assessment of a variety of clinical breast specimens. Specimens were evaluated with a table top micro-CT scanner, Skyscan 1173 (Skyscan, Belgium), with a 40–130 kV, 8 W X-ray source. Skyscan software for 3D image analysis (Data-viewer and CTVox) was employed to review 3D graphics of specimens. Scanning for 7 min and another 7 min for image reconstruction provided the desired resolution for

breast specimens. Breast lumpectomy specimens, shaved cavity margins, mastectomy specimens, and axillary lymph nodes were imaged by micro-CT. The micro-CT images could be rotated in all directions and cross sections of internal portions of specimens could be visualized from any angle. This provided information about spatial orientation of masses and calcifications relative to margins in intact lumpectomy specimens. Micro-CT is a potentially useful tool for assessment of breast cancer specimens, allowing real-time analysis of tumor location in breast lumpectomy specimens or shaved cavity margins. Micro-CT may also be useful for assessing sentinel lymph nodes and mastectomy specimens.

Keywords Micro-CT · Breast cancer · Lumpectomy margins · Lymph nodes · Real-time analysis

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Background

Specimen radiography was first described in 1966 as part of needle-localized excision of non-palpable but mammographically visible breast lesions [1]. Specimen radiography reliably confirms excision of a targeted non-palpable breast lesion, and is the standard of care in needle-localized excisions [2].

Specimen radiography is also used for margin evaluation of excised specimens. If a particular margin appeared “close” or “positive” on specimen radiography, additional tissue could be excised from the surgical cavity during the same lumpectomy procedure. Several studies have looked at the use of conventional specimen radiography for intraoperative margin assessment of excised breast specimens [3–6]. Accuracy of margin assessment has been variable, however, due to limitations with specimen

orientation, 2-dimensional (2D) images of a 3-dimensional (3D) specimen, and a high rate of nonspecific findings such as dense parenchyma and architectural distortion [4–6].

Micro-computed tomography (micro-CT) is a novel technology for imaging breast tissue, especially small specimens, with spatial resolution possible to $<1\ \mu\text{m}$ [7]. Micro-CT provides non-invasive, 3D imaging. To date, there has been limited use of micro-CT for imaging tumor specimens, and only a few small studies have used micro-CT to evaluate the structure of excised breast tissue [8–12]. Micro-CT has been reported to distinguish malignant breast masses from fibrous breast tissue, and benign from malignant calcifications [8, 9].

In this study, we used micro-CT to image a variety of breast cancer specimens including lumpectomy specimens and lumpectomy shaved cavity margins (SCM), mastectomy specimens, and axillary lymph nodes. We sought to determine the ability of micro-CT to produce clinically accurate images of the internal structure of breast specimens. In addition, we examined the feasibility of using micro-CT for real-time, intraoperative assessment of breast excision specimens.

Materials and methods

This study was approved by the Massachusetts General Hospital Institutional Review Board. Prospective consent, which allowed for additional imaging of excised breast tissue, was obtained from patients undergoing surgery for breast cancer.

Following excision, fresh specimens were placed in a plastic container and imaged using a table top micro-CT, Skyscan 1173 (Skyscan, Belgium), with a 40–130 kV, 8 W X-ray source. The field of view was 14 cm; therefore, this was the maximum specimen diameter that could be imaged. For wire-guided excisions, conventional specimen mammography was performed first. Once excision of the target lesion was confirmed, the wire was removed from the specimen prior to micro-CT to minimize artifact. In the case of SCM, up to three specimens could be imaged simultaneously by layering the margins within the plastic container, separated by Styrofoam [13]. Specimens were scanned using a 7-min scanning protocol. The micro-CT scanner rotated specimens 360° with an incremental rotation step of $0.40\text{--}0.80^\circ$; one or two 2D transmission images were obtained at each rotation step. All 2D cross sections were also fully reconstructed using Skyscan's NRecon program, which took an additional 7 min. To review 3D graphics of the specimens, Skyscan software for 3D image analysis (DataViewer and CTVOx) was employed. After micro-CT examination, routine histological examination was performed.

Reconstructed images underwent a blinded evaluation by one of two physicians (R.T. and L.F.) for radiographic signs of involvement with non-invasive and invasive breast cancer, including clustered microcalcifications and spiculated masses. Lumpectomy margins were considered radiographically positive if microcalcifications or masses were present within 0.2 cm of the specimen edge. SCM were similarly evaluated for the presence of malignancy. Pathologic margin status was determined by examination of permanent paraffin-embedded sections by breast pathologists. In this study, histologically positive margins (cancer cells touching the inked margin's surface) and close margins (cancer cells within 2 mm of the inked margin's surface) were grouped together as pathologically involved margins. Margin status as determined by micro-CT was compared to margin status on standard histopathology analysis. Maximum tumor size based on the micro-CT images was compared to tumor size on pre-operative imaging and gross tumor size by histopathological examination.

Results

A total of 71 breast lumpectomy specimens, 25 separate SCM specimens, three axillary lymph node dissection specimens, and four mastectomy specimens were imaged by micro-CT. All imaged specimens were from female patients with a known diagnosis of breast cancer. Patient ages ranged from 33 to 82 years, with a mean age of 59.

Micro-CT clearly visualized orienting sutures in excised specimens, allowing accurate orientation of tumor masses and calcifications within the specimen and relative to specimen margins. The micro-CT system provided virtual "sectioning" of the specimen in multiple planes, which allowed margin evaluation in all directions (Fig. 1). Microcalcifications within specimens were clearly visualized. The spatial orientation of masses and calcifications with respect to the edge of the specimen was clearly determined by rotating specimen images in all directions and examining cross-sectional images. Figure 2 illustrates how rotation of specimen images provides precise identification of DCIS-associated calcifications at a specimen margin, which is not possible with conventional specimen imaging. Images of internal cross sections of intact specimens allowed localization and definition of the closest margin of a mass (Fig. 3).

Micro-CT was also able to provide detailed 3D images of the internal structure and vasculature of excised axillary lymph nodes. Benign lymph nodes had a regular oval contour and homogeneous internal appearance, while lymph nodes that contained metastatic tumor deposits had an irregular profile and a more heterogeneous internal structure, sometimes containing calcifications (Fig. 4).

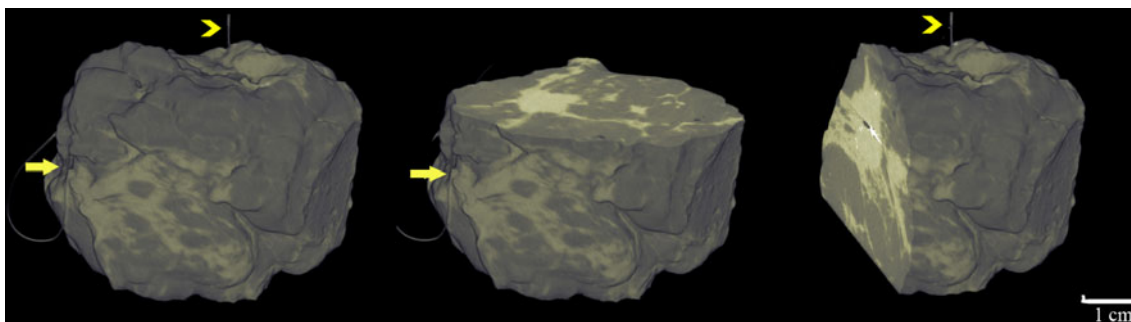


Fig. 1 Multiplanar images from micro-CT imaging of a breast lumpectomy specimen. Micro-CT allows virtual sectioning of specimen in multiple planes. Orienting sutures: short superior (*greater than sign*) and long lateral (*arrow*)

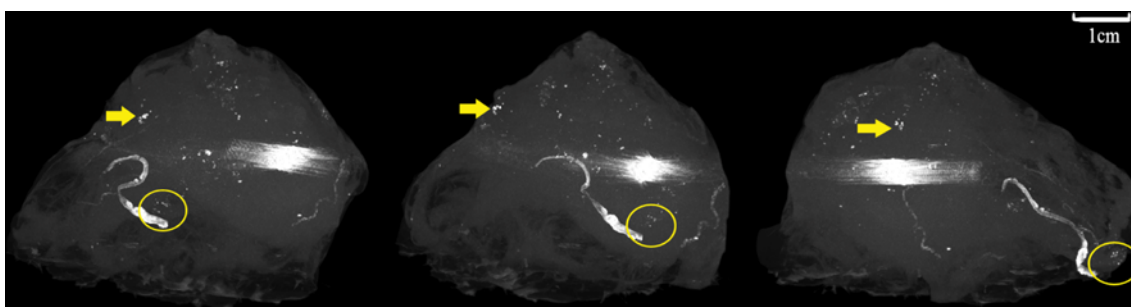


Fig. 2 Rotating the specimen allows localization of targeted microcalcifications relative to specimen margins. *Arrows* calcifications group 1. *Circle* calcifications group 2. A biopsy clip is seen as a large white spot and a calcified blood vessel is also seen

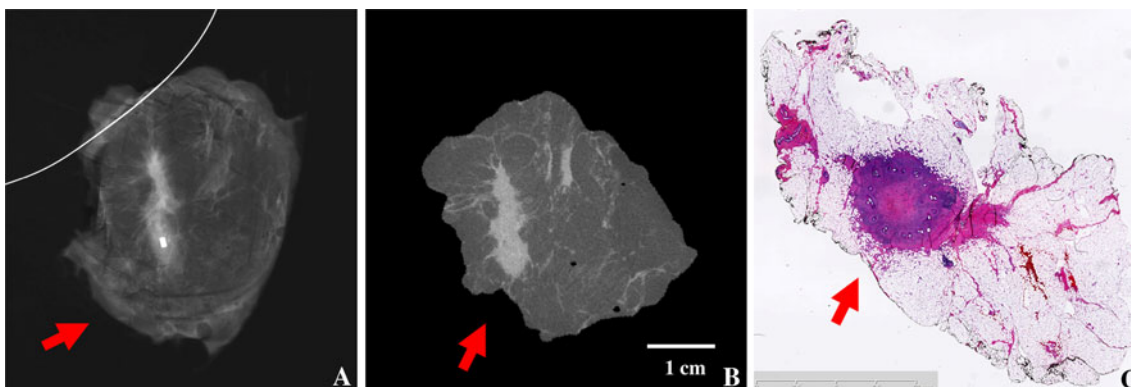


Fig. 3 **a** Tumor mass in lumpectomy specimen radiograph appears distant from the margin (*arrow*). **b** Cross-sectional micro-CT image shows that mass is actually close to the margin (*arrow*).

c Histopathology shows invasive carcinoma present 0.15 cm from the inked margin, consistent with micro-CT finding

Micro-CT was also used to evaluate separately excised lumpectomy SCM. With the high resolution of micro-CT images, small tumor masses were clearly seen against background breast tissue. Micro-CT also allowed detailed assessment of microcalcification morphology, making it possible to distinguish benign and malignant microcalcifications.

Intact mastectomy specimens up to 14 cm in diameter were also imaged with micro-CT. Nipple–areola complex pathology could be visualized and the locations of multicentric tumor masses were seen within intact mastectomy specimens. In addition, micro-CT was able to distinguish

benign from malignant masses within mastectomy specimens (Fig. 5).

Discussion

Microscopically clear lumpectomy margins are essential in breast-conserving therapy for breast cancer. Unfortunately, 18–59 % of contemporary lumpectomy patients will have lumpectomy margins that are microscopically involved by tumor and require re-excision [14–17]. New approaches to

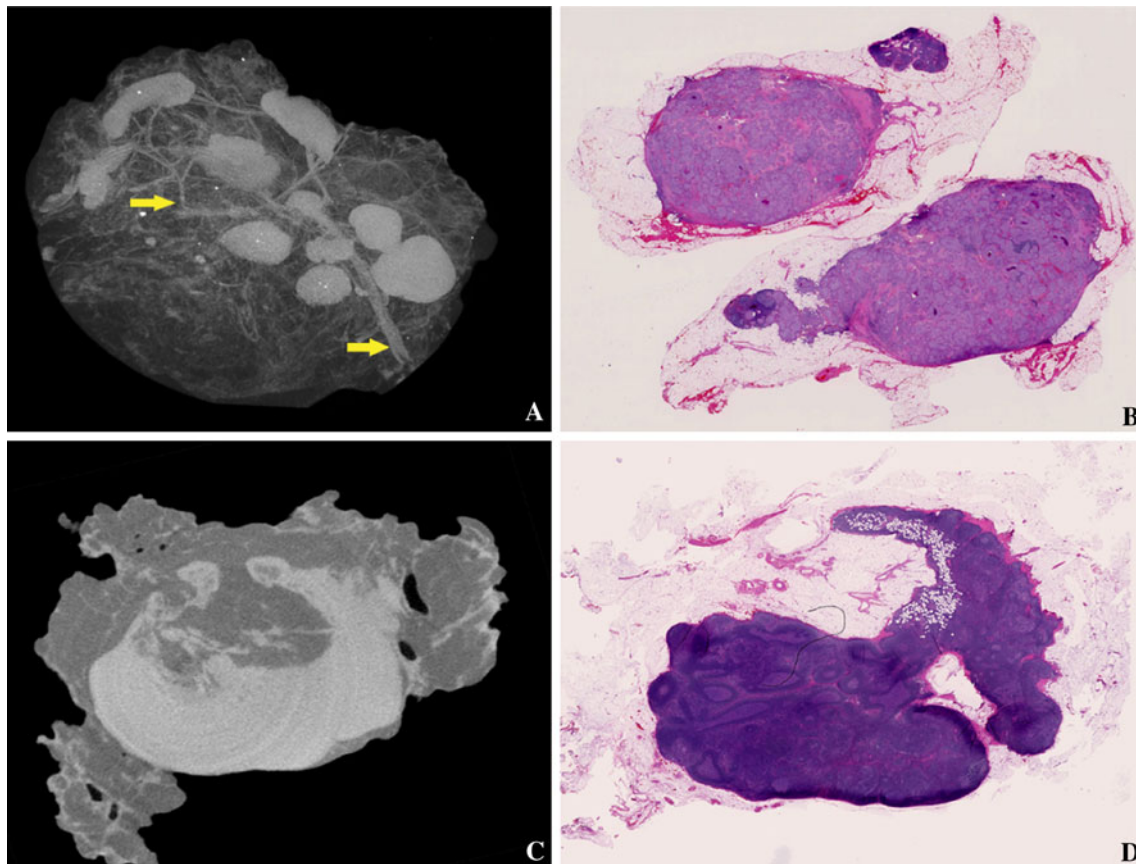


Fig. 4 **a** Micro-CT showing the structure and fine vessels (*arrow*) of axillary lymph nodes, seen as solid, round structures connected by an arborizing network of vessels (*arrow*) **b** corresponding histopathology

slide shows two lymph nodes entirely replaced by metastatic carcinoma **c** micro-CT of a benign sentinel lymph node **d** corresponding histopathology slide showing benign node histology

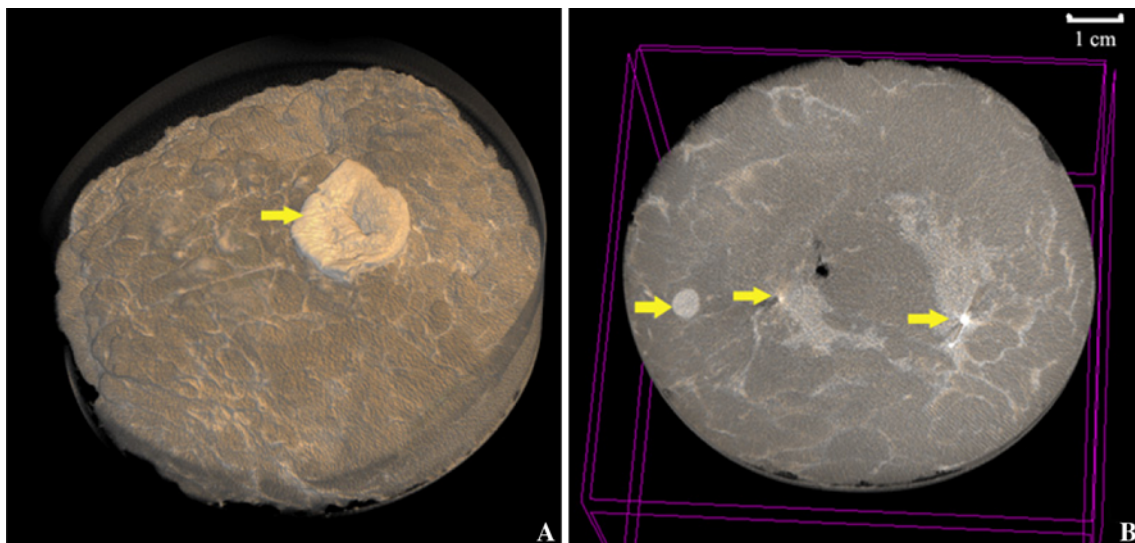


Fig. 5 **a** Surface image of a mastectomy specimen with a retracted and inverted nipple (*arrow*) **b** micro-CT mastectomy specimen deeper cross-sectional image showing histologically confirmed multifocal

carcinoma seen as ill-defined dense areas containing biopsy clips (*center and right arrows*). A well-circumscribed round mass is also seen, histology confirming a benign fibroadenoma (*left arrow*)

identify and re-excise these positive lumpectomy margins intraoperatively are needed. Specimen radiography is one of the most commonly employed techniques used by

surgeons to assess the adequacy of tumor excision, but conventional specimen radiography has not proved reliable for predicting margin status [4–6]. With standard specimen

mammography, margin assessment is limited by the 2-dimensional views produced. While some physicians have attempted to mimic a 3D assessment by obtaining additional specimen mammograms images after rotating the specimen, this has not increased the accuracy of margin assessment [5].

Micro-CT has previously been used in orthopedic research to analyze the architecture of bones in osteoporosis, osteopenia, bone malformations, and bone tumors [18–21]. Data on the use of micro-CT for breast tumor imaging is limited [8–12]. Nishide et al. [11] studied breast specimens containing microcalcifications, and reported that micro-CT was useful for understanding breast structure and patterns of microcalcifications. Gufler et al. [8] used micro-CT to evaluate breast core biopsy specimens from 15 patients and compared micro-CT images to the corresponding histological slides. They concluded that micro-CT is feasible for the differentiation of breast tissue components in core needle biopsy specimens.

In this study, we report the feasibility of using micro-CT to examine structural and anatomic features of breast cancer specimens. Micro-CT was able to create multiplanar, cross-sectional images of the internal structure of intact lumpectomy and shaved cavity margin specimens, allowing for evaluation of margins in all directions. In contrast to specimen mammography, micro-CT clearly visualized orienting sutures on specimens, which could further aid margin assessment and allow better identification of areas of residual tumor for targeted margin re-excision. These aspects of micro-CT specimen imaging make it a promising technology for intraoperative margin assessment, with the potential to reduce the need for second re-excision procedures.

We have previously applied micro-CT techniques to other aspects of breast lumpectomy margin assessment. In one study, we assessed the ability of micro-CT to determine tumor size in intact lumpectomy specimens, compared with tumor size as measured on standard histopathology [22]. In another study, we compared accuracy of margin assessment by micro-CT with evaluation by conventional specimen mammography in 46 lumpectomy specimens. Micro-CT identified 32 of 55 positive margins (specificity 93 %, sensitivity 60 %) while specimen mammography identified only 20 of 55 positive margins (specificity 96 %, sensitivity 36 %) [23]. In another study, micro-CT was used to evaluate separately excised lumpectomy SCM. A total of 25 SCM from 6 lumpectomies were imaged with micro-CT. In this small dataset, SCM status by micro-CT was concordant with histopathology in 23 of 25 cases (92 %) [13]. The high concordance rates of micro-CT with histopathology in these studies suggest that micro-CT is a promising tool for margin assessment.

Our study is the first to report the use of micro-CT to evaluate axillary lymph nodes and intact mastectomy

specimens in breast cancer patients. Micro-CT provided detailed anatomic images of axillary lymph nodes, and was able to clearly demonstrate structural differences between benign nodes and nodes containing metastatic tumor. Micro-CT imaging of whole mastectomy specimens allowed views of internal “slices” in all three dimensions. The ability to image an intact mastectomy specimen might be useful for multicentric tumors, where the number, location, and size of the individual tumors could be determined prior to gross pathological examination. Our micro-CT scanner could image specimens up to 14 cm in diameter, which could accommodate many, but not all, mastectomy specimens.

A potential limitation of micro-CT is the time it takes for image acquisition and reconstruction. Current scanning technologies require longer scanning times to generate higher resolution images. We found that a 14-min protocol generated images of sufficiently high quality to distinguish tumors from benign tissue in most cases. Although this time may be longer than ideal for intraoperative feedback, small changes in surgical workflow may help avoid delays in completion of surgery. For example, since adoption of ACOSOG Z0011 trial results has reduced use of frozen section and immediate axillary dissection for positive sentinel nodes [24], the lumpectomy could be performed first, allowing time for micro-CT scanning of the lumpectomy specimen while the sentinel node biopsy is performed.

Micro-CT units are self-shielded, and compact enough to be placed near the operating room suite, potentially reducing specimen transport time. We are currently conducting a study with our micro-CT dataset to determine whether surgeons can be trained to perform an initial interpretation of micro-CT images for rapid intraoperative margin assessment. Improvements in micro-CT technology may ultimately allow for more rapid image acquisition that comes closer to the goal of accurate, real-time margin assessment.

Conclusions

Micro-CT is a promising tool for evaluation of breast cancer specimens. It allows real-time identification and excision of tumor at lumpectomy margins, which could reduce the rate of second surgical procedures for involved margins. Unique features of micro-CT include the ability to create multiplanar, cross-sectional images of intact excised breast specimens that can be reconstructed to provide detailed anatomic and spatial information. Micro-CT may also be useful for imaging axillary lymph node and mastectomy specimens.

Conflict of interest The authors have no conflicts of interest to disclose.

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