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RESEARCH ARTICLE

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A feasibility study of a portable intraoperative specimen imaging X-ray system based on carbon nanotube field emitters

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Abstracts
When breast cancer is surgically removed, a rim of normal tissue surrounding the tumor is also removed. This rim of normal tissue is called a margin and is studied by a pathologist to determine whether or not all tumor was removed. The pathologist achieves this by cutting the surgically removed tissue into thin slices and observing each slice under a microscope. This process is time-consuming. Here, we investigate the feasibility of using a portable carbon nanotube (CNT)-based X-ray system for in situ detection of the presence of tumor cells in the surgical margin. Using the proposed technique, we successfully obtain X-ray images, which clearly show cancer masses and microcalcifications. This feasibility study shows that portable CNT-based X-ray systems are promising candidates for next-generation in situ pathological examinations.

KEYWORDS
breast cancer, carbon nanotube emitter, field emission, pathological study, surgical margin, tumor, X-ray imaging

1 | INTRODUCTION

Nonpalpable breast cancer with or without microcalcifications is mostly diagnosed by mammography (MMG).[1,2] If the diagnosis falls under BI-RADS (Breast Imaging-Reporting and Data System) category 4 or 5, it is considered as a suspicious lesion and biopsy or surgical excision is recommended.[3,4] The main treatment for the removal of malignant breast tumors is considered to be surgery.[1] Preceding the surgery, locations of malignant masses on breast tissues are confirmed through a mammogram. Depending on the sizes and distribution of the lesions, the patient usually undergoes partial or complete resection of breast tissue with a rim of normal tissue around it. This rim is called a margin and helps to ensure complete removal of cancer cells, thereby avoiding the risk of local recurrences.[2]

The margin is described as negative when a pathologist finds no cancer cells in a distance at least 0.2 cm from the edge of the tissue, suggesting that all of the cancer has been successfully removed, or positive when the pathologist finds cancer cells in a distance less than 0.2 cm from the edge, suggesting that all of the cancer has not been removed (Figure 1).[5–7] The process of checking the surgical margin, known as histopathology, is time-consuming, as the removed tissue is taken out of the operating room and delivered to a pathologist who will cut the tissue into thin slices and observe each slice under a microscope.[1,3,7] During histopathology, the surgery is put to a halt and it usually takes at least an hour to get the results.[8,9]

To save time during surgery, the use of portable intraoperative X-ray systems to take images of the removed tissue inside the operating room is becoming popular.[8–11] These X-ray systems are based on a filament, the cathode, which is heated to emit electrons by thermionic emission. The emitted electron beam is targeted to a reflection-type metal, the anode, which generates an X-ray beam in the direction perpendicular to the direction of the electron beam.[12] However, slow response of thermionic processes prevents filament-based X-ray systems from being fully digitalized. The slow response of thermionic emitters is due to the lag time associated with the time required to preheat the filament.[13]

To meet the needs of the emergence of ever more demanding medical inspection techniques, technologies with faster temporal response and better design freedom than thermionic emitters should be developed. Recently, field emitters based on carbon nanotubes (CNTs)[14] and silicon emitters[15] are being developed to replace filaments for these demanding applications. Researchers at the North Carolina University developed a stationary, CNT-based multi-X-ray source for digital tomosynthesis that outperformed the conventional 2D MMG machine in visualizing microlcalcifications.[16–18] Therefore, the focus in medical imaging is now toward the replacement of thermionic emitters with field emitters for next-generation X-ray systems.

Here, we investigate the feasibility of using a portable CNT-based X-ray system to take images of the removed tissue inside the operating room. In CNT-based X-ray systems, the cathode is made of CNTs, which emit electrons via field emission (FE). CNT field emitters can swiftly turn on and off, allowing the generation of short pulsed X-ray radiation.[19] Electrons can be extracted from CNTs at room temperature, allowing the formation of cold cathode X-ray sources. These attributes lead to reduction in power consumption, robustness, and high-resolution

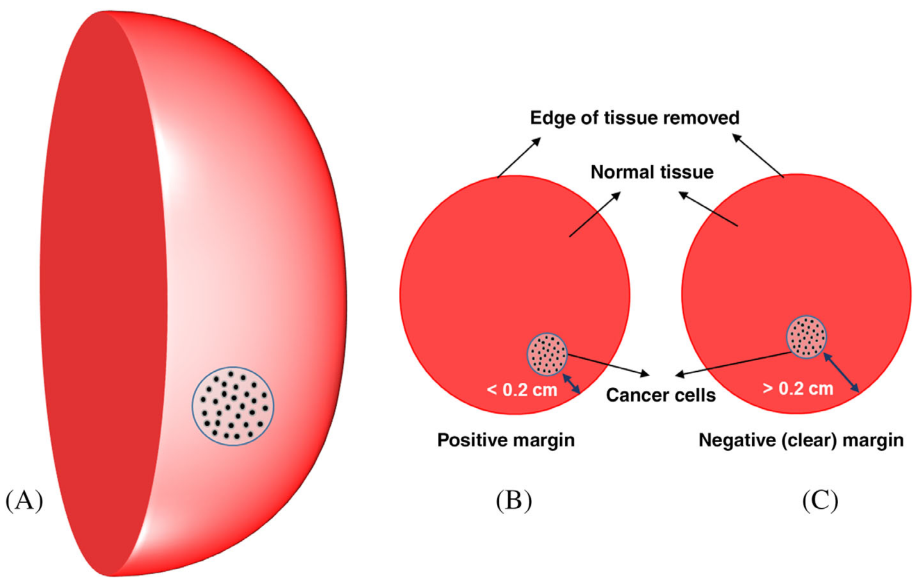

FIGURE 1 Schematic diagram for (A) the removed breast tissue with calcification, (B) the positive surgical margin, and (C) the negative surgical margin [Color figure can be viewed at wileyonlinelibrary.com]

image with a low dose. Additionally, miniaturized CNT-based X-ray source designs are possible, as the CNTs can be fabricated on substrates with various shapes and sizes, which gives developers a lot of design freedom.[13,20,21]

2 | MATERIALS AND METHODS

2.1 | Materials

Two postoperative breast specimens used in this study were obtained under the supervision of a surgeon. Before the surgery, cancer cells or malignant masses in both breast specimens were confirmed by standard MMG. The study was performed on patients who underwent breast-conserving surgery for breast cancer. Biopsy was performed in patients who showed suspicious calcified lesions in MMG as shown in Figure 2(A). The MMG in Figure 2(A) shows aggregated tumor masses with diameter ≅1 cm.

After partial excision, metal clipping was performed at 3 o'clock and 12 o'clock of the removed specimen to indicate the orientation of the surgical specimen as shown in Figure 2(B), which represents the breast specimen 1. Similar procedure was followed to obtain breast specimen 2. Afterward, these specimens were brought to a certified X-ray room where the proposed CNT-based X-ray system was installed, and X-ray images were taken under the supervision of a radiologist. Finally, the specimens were sent to a pathology laboratory for histological examination after taking the X-ray images.

2.2 | Characterization of CNT field emitter

The CNTs were grown using a direct current plasma-enhanced chemical vapor deposition explained in detail elsewhere.[22] To confirm uniform growth of CNTs on the metal substrate, FE scanning electron microscope (SEM) (SU-70, HITACHI Japan) was used to take the high resolution images. To increase emission sites and stabilize the FE, an electrical aging process was carried out by taking[23] repeating FE measurements for 100 cycles using a computerized program, which swept the biased voltage from 0 to 1900 V.

The FE properties of the CNT emitters were measured in portable open-type X-ray chamber with the triode configuration at base pressure of 3.0×10^{-7} Torr. The CNT-based open-type X-ray system was preferred over a small X-ray tube to ensure ultra-high vacuum condition inside the system.[24,25] The high vacuum condition ensures a stable electron beam production and increases the life time of emitter. In the open-type X-ray system, an operator can change the distance between cathode and anode, which ultimately helps in controlling the focal spot of the beam producing high resolution X-ray images.[25]

The triode configuration was preferred over the diode configuration to have control over the electron emission at fixed anode voltage. The gap between the gate and cathode was maintained at 370 μm. Spellman SL300 (Spellman High Voltage Electronics Corporation, New York, NY, USA) was used to measure the anode current and as an anode voltage source. During the FE process, the anode voltage was fixed below 5.5 kV. To measure the gate current and for the gate voltage source, the Stanford research PS350 (Stanford Research Systems, CA, USA) was used. For the cathode current measurement, Keithley 6485 (Keithley Instruments, Inc, OH, USA) was installed between the emitters and the ground.

2.3 | Operating of open-type X-ray system

Figure 3(A,B) shows 3D solid work rendering setup of the potable open-type 4.5 inch X-ray system used in this study. Figure 3(C) shows the real lab setup of the system. Electrical feedthroughs for a high-voltage anode and

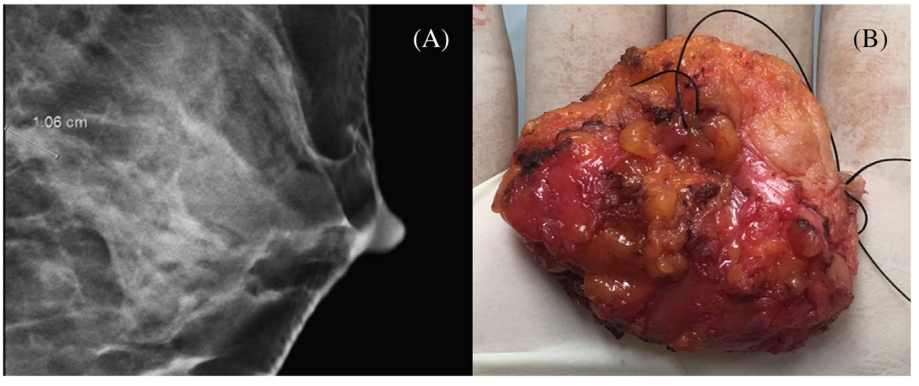

FIGURE 2 (A) Standard mammogram taken before the surgery and (B) the optical image of surgically removed breast tissue (specimen) [Color figure can be viewed at wileyonlinelibrary.com]

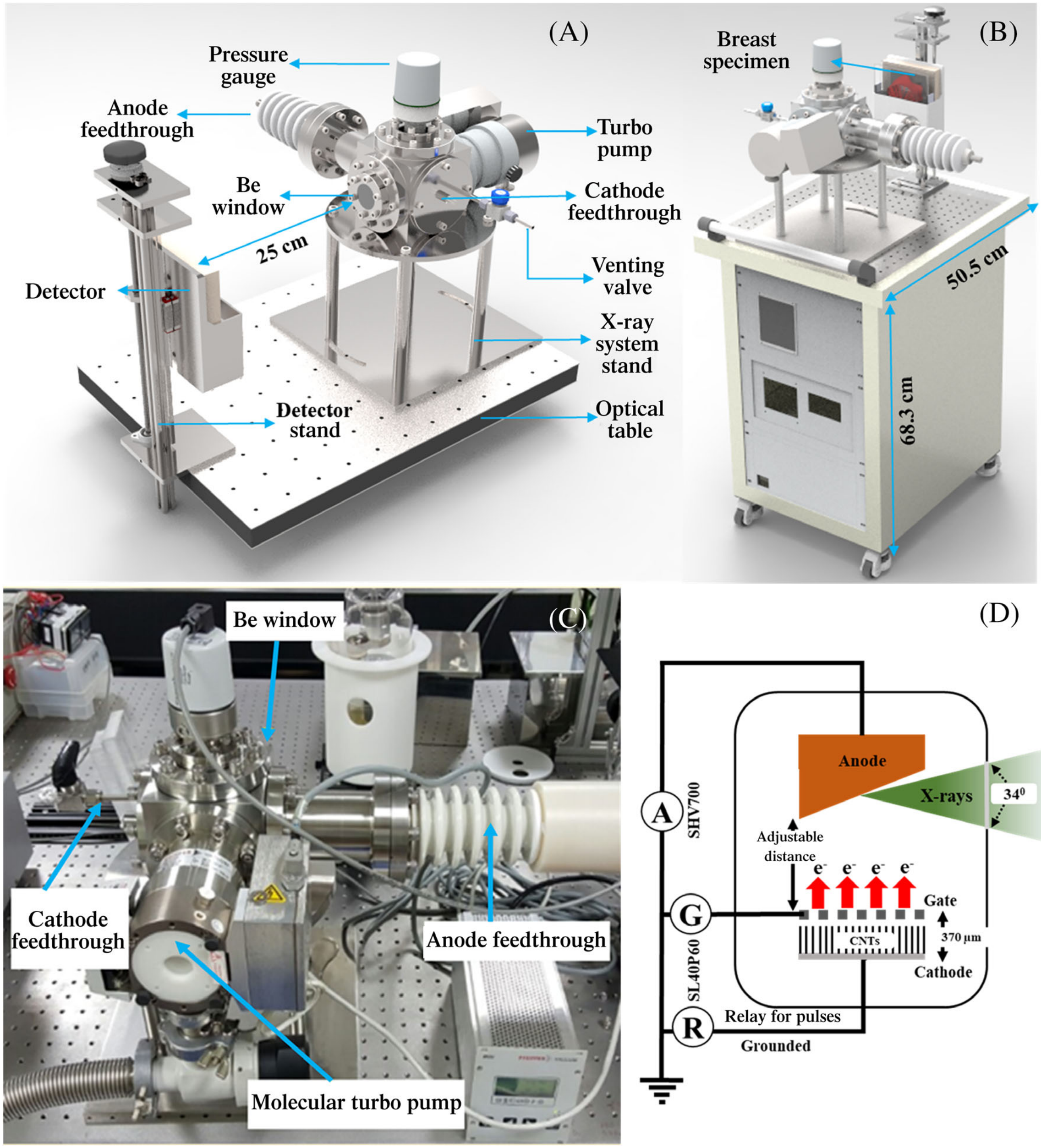

FIGURE 3 (A, B) 3D solid work diagrams; (C) an optical image of carbon nanotube (CNT) X-ray inspection system for screening the surgical margin of breast specimen; and (D) the schematic diagram of X-ray system and field emission measurement test [Color figure can be viewed at wileyonlinelibrary.com]

cathode sources were located on opposite sides. A beryllium (Be) window with a thickness of 0.254 mm was used as the X-ray filter and molecular turbopump (TMU 071P) was used to achieve the required vacuum conditions. A full range gauge (PKR251) was installed at the top to measure the pressure inside the chamber.

Figure 3(D) shows a schematic setup of the triode configuration. An electron gun was connected to the cathode feedthrough and had a diameter of 16 mm. The electron gun consisted of a focusing gate and the cathode. The cathode consisted of CNTs grown on a metal substrate with total emission area of 0.1377 cm^2. The gate was meshed and had regular hexagonal geometry with side length of 360 μm, an area of 0.00336 cm^2, and aperture ratio of 89.7%. The gate and cathode were separated by a ceramic spacer and maintained at a distance of 370 μm apart. The focusing electrode had length of 10 mm, open width of 3 mm, and thickness of 2.5 mm.

The anode, which was made up of tungsten embedded on copper, had a radius of 5.5 mm and cutoff angle of 17^0. The cutoff angle of 17^0 helps to produce the X-ray emission with field coverage of 34^0. Two high-voltage power sources were used separately for the anode and gate. The gate voltage was supplied by the Spellman High Voltage SL40P60/NSS/100 power supply and the anode voltage by the SHV700 power supply. The cathode was grounded with relay to operate in pulse mode. A pulse width of 5 s was set, during which an X-ray image of the breast specimen was taken.

The cathode and the anode were installed opposite to each other, so that X-ray emissions could be transmitted horizontal to the ground through the Be window. The detector (RAD icon, 0889, Teledyne Rad-icon Imaging Corp, CA, USA) with 1024 × 512 pixels was placed 25 cm away from the Be window with the help of a detector stand. The breast specimen was put inside a transparent plastic bag and attached to the detector while taking X-ray images. During X-ray emission, the turbopump was maintained at a base pressure of 4×10^{-8} Torr.

3 | RESULTS AND DISCUSSION

3.1 | Performance of CNT field emitter

Figure 4(A) shows a SEM image of CNTs taken at 5000× magnification. The CNTs were not vertically aligned but rather appeared as randomly grown spaghetti on a black metal plate. Average diameter of the CNTs was approximately 200 nm.

Figure 4(B) shows current–voltage (I-V) characteristics of the CNT field emitter. Cathode current of approximately 1.1 mA and anode current of 0.82 mA were obtained at gate electric field of 5.1 V/μm. Anode current was measured by regulating the gate voltage in dc mode. Gate leakage to anode current ratio was below 20%.

Figure 4(C) illustrates the stability of the CNT emitter for 10 h in DC mode. The initial cathode current was 0.9 mA at gate electric field of 5 V/μm. During the stability test, current decreased from 0.9 to 0.65 mA because of internal arcing or stress from the electrical aging process. The current remained stabled afterward, with maximum and minimum values of 0.67 and 0.63 mA. This result indicates high stability of CNT field emitters. Note that breast specimen X-ray imaging systems available in the market usually have anode current specifications of only 0.3 mA.

To evaluate the resolution of the X-ray system, an X-ray image of the line pair phantom was taken. Figure 4 (D) shows an X-ray image of line pair phantom Type 81 CN 75485 0.05 mm Pb at an anode voltage of 55 kV with current exposure time of 1 mAs. Limiting spatial resolution of the X-ray system used herein was 3.4 lines per mm (inset of Figure 4D). This is much lower than the 10–13 lines per mm of resolutions for filament-based

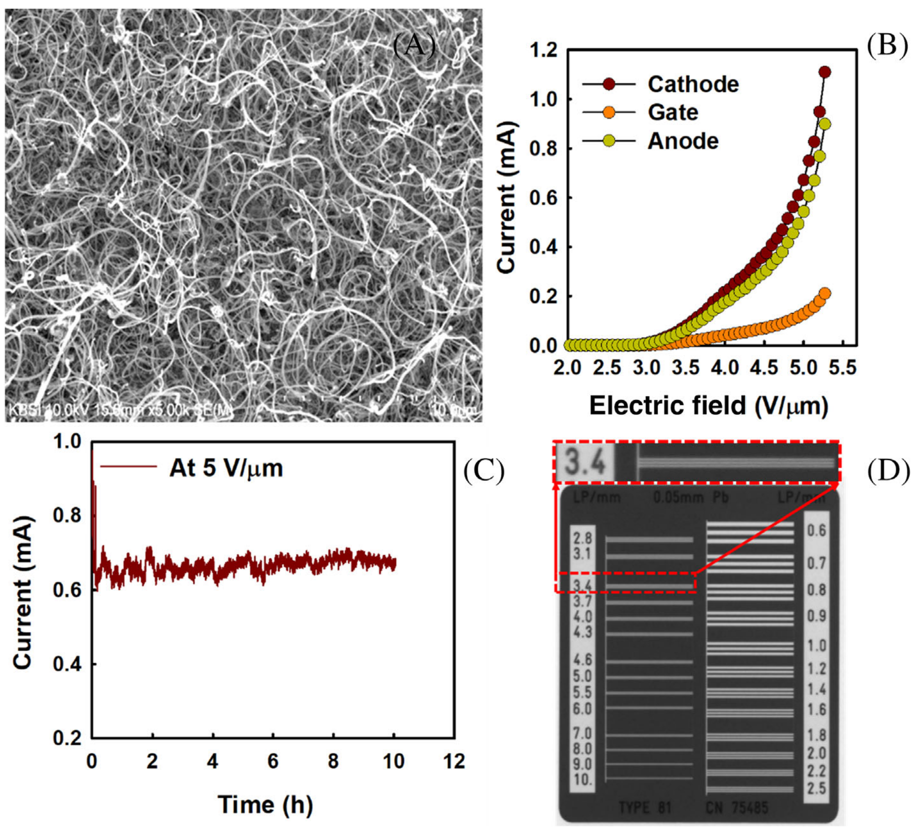

FIGURE 4 (A) A scanning electron microscope (SEM) image of carbon nanotube emitter on alloy substrate; (B) the current–voltage (I-V) characteristic of carbon nanotube (CNT) field emitter; (C) the stability of CNT field emitter used in X-ray system; and (D) an X-ray image of line pair phantom, inset shows the limiting spatial resolution of 3.4 lines per mm [Color figure can be viewed at wileyonlinelibrary.com]

intraoperative specimen X-ray system available in the market.[26] However, this is just a feasibility study and further research is warranted to improve the resolution.

3.2 | X-ray images of breast specimens

The anode voltage was varied from 25 to 40 kV to acquire X-ray images of the breast specimen 1 under the guidance of a professional radiologist. Compared to other radiographic techniques, MMG is typically performed at lower kilovoltage because intramammary tissues are not dense[27] and most of the radiation is absorbed by high density cancer masses. Normally, the required range is 25–50 kV, depending on the anode material and breast density type.

Figure 5 shows X-ray images with a magnification factor of 1.5× of the breast specimen 1 (see Figure 2B) taken at different accelerating voltages. In Figure 5(A–C), a black surgical thread (see Figure 2B) is visible at the left upper side of the X-ray images. However, when the anode voltage was increased to 40 kV, small details of the specimen disappeared due to high intensity X-rays from Tungsten target. From these images, radiologists confirmed that 5 s of exposure time under anode voltage of 30 kV and corresponding current of 0.1 mA, was sufficient to produce images with the appropriate brightness and contrast. Malignant breast tumor without calcifications (indicated by red circles in Figure 5) was visible in the images.

From the results published in a conference proceeding by our group at SPIE 2018 Medical Imaging,[28] we were able to detect small microcalicifications present in the breast specimen 2 using the proposed X-ray system. Figure 6(A) shows an optical image of the breast specimen 2 after breast conserving surgery. Figure 6(B) shows the X-ray image of the breast tissue with a 3× magnification factor. Microcalcifications were spread over a relatively large area in the excised specimen. This suggests that the CNT-based X-ray source was able to detect micrometer-sized microcalcifications.

Compared to the CNT-based X-ray source presented herein, Filament-based X-ray systems available in market have better spatial resolution. Therefore, further research is needed to improve the resolution of CNT-based sources, using techniques such as micro-focusing.[29]

3.3 | Limitations and further work

As this study is a preliminary investigation on the possibilities of using a CNT-based X-ray source to image breast specimens, it still has limitations that require further studies. First of all, it is an open type X-ray system which is connected to a large vacuum pump. As a result, it is not as compact as the commercial specimen imaging systems available in the market. Therefore, this technology needs to be converted to a sealed type X-ray tube, preferably enclosed by a ceramic or glass envelope. Second, the

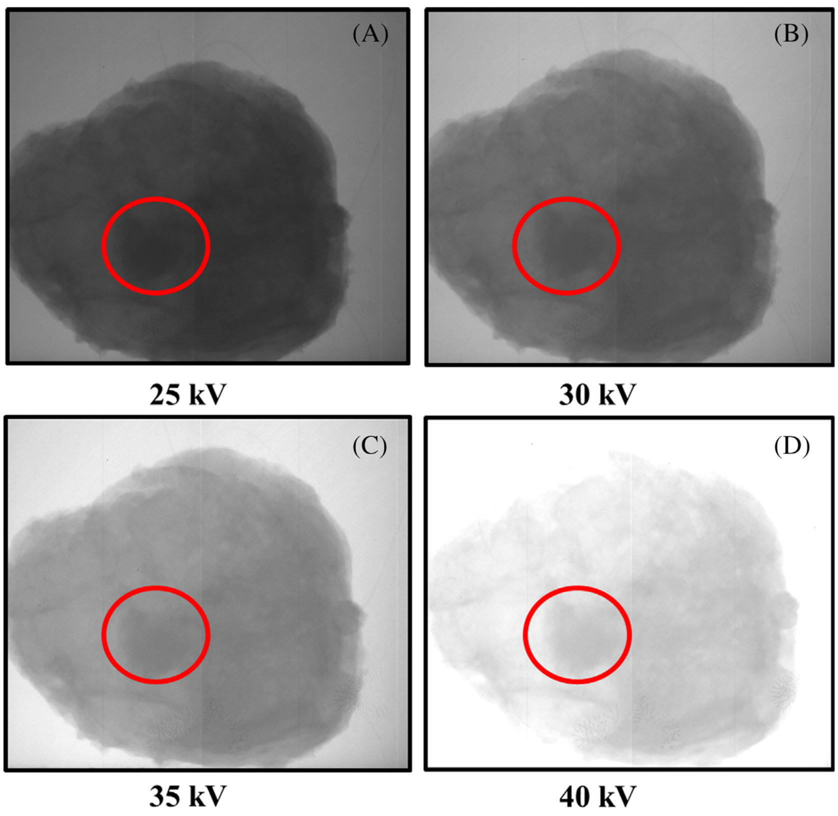

FIGURE 5 X-ray images of surgically removed breast tissue taken at different accelerating voltages. The solid dense mass under the red circle shows the malignant tumor cells [Color figure can be viewed at wileyonlinelibrary.com]

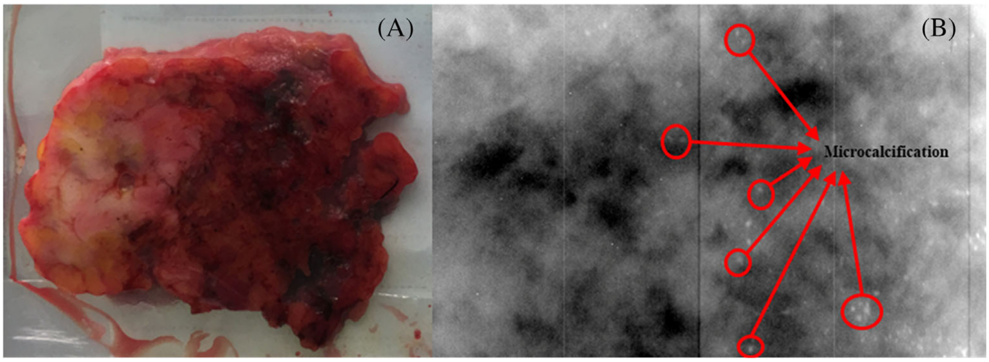

FIGURE 6 (A) An optical image of breast specimen and (B) the X-ray image of surgically removed breast specimen showing the microcalcifications[28] [Color figure can be viewed at wileyonlinelibrary.com]

resolution of the X-ray system used in the study is lower than what is available in the market. Thus, further work directed toward higher resolution such as cathode size reduction is warranted. The use of CNT field emitters also has the potential to revolutionize X-ray imaging. In particular, it enables the use of digitally controlled multiple X-ray sources in a single X-ray system to develop a stationary 3D X-ray system. This work is underway and will be reported in a future publication.

4 | CONCLUSION

In this feasibility study, we demonstrated the working of a CNT-based FE, open-type X-ray system for imaging of postoperative breast specimens. The X-ray images taken by the intraoperative CNT-based X-ray system have good spatial resolution to diagnose micrometer-sized calcifications. This system provides an alternative to filament-based X-ray systems. Due to its low power consumption and active control switching, it could be a better choice for portable intraoperative specimen imaging X-ray systems. This study could pave the road for future researches to develop CNT-based X-ray systems for application in areas such as dental, fluoroscopy, or breast cancer biopsy.

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CONFLICT OF INTEREST

The authors declared no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Study concept and design: Jehwang Ryu. *Data acquisition*: Amar Prasad Gupta, Jaeik Jung, Wooseob Kim, Jongmin Lim, Junyoung Park. *Analysis and interpretation of data*: Namkug Kim, Seung Hoon Kim, Jeung Sun Ahn, Moon Shik Chae, Yeong Heum Yeon. *Drafting of the manuscript*: Amar Prasad Gupta, Mallory Mativenga. *Obtained funding*: Jehwang Ryu, Seung Jun Yeo. *Study supervision*: Jehwang Ryu and Beom-Seok Ko.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author (J.R., M.M., and B. K.) upon reasonable request.

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