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The main objective of this investigation is to determine the feasibility and value of the intraperative use of a small field of view (FOV) camera gamma camera for sentinel lymph node (SLN) localization in breast cancer patients. Two cameras, on with a 1" x 1' FOV and one with a 5" x 5" FOV are being investigated. Clinical experience with 14 subjects using the 1 in x 1 in FOV and 15 subjects using the 5 in x5 in FOV suggests that the 5 x 5 FOV is more valuable for SLN localization in breast cancer patients than is the 1" x 1" FOV. The task of verifying the content of two databases one consisting of data form 121 breast cancer patients and the other consisting of data from 50 was carefully done. Data from the database consisting of data from 50 was carefully done. Data from the database consisting of 50 patients were presented at the 8th Congress of the World Federation of Nuclear Medicine and Biology 2002 in Santiago, Chile by the senior nuclear medicine technologist at Atlanta VAMC. The data for the other database are currently being analyzed statistically to determine correlation factors. Initial assessment of the data of the 15 subjects images with 5" x 5" FOV camera suggests use of the device is feasible and of value for SLN localization in cases which preoperative imaging is not performed.

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INTRODUCTION:

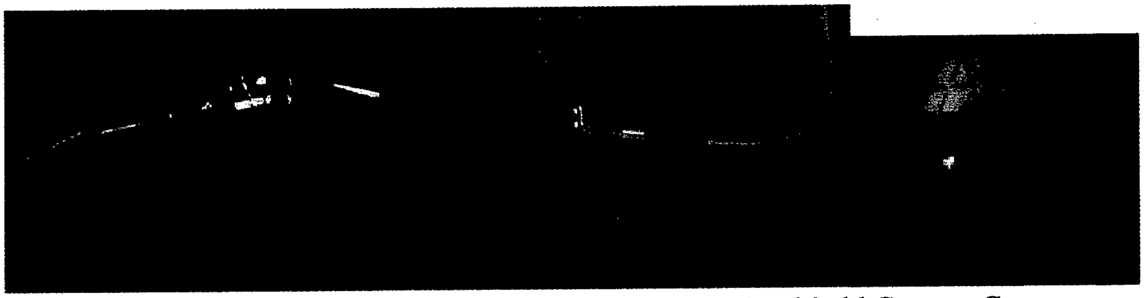
Sentinel lymph node (SLN) biopsy is the standard of care for the staging of some melanoma patients and is likely to soon be the standard of care for some breast cancer patients. There are several approaches to SLN resection, some are more extensive than others. Some approaches use preoperative nuclear medicine imaging and intraoperative gamma counting. Others rely solely upon intraoperative gamma counting. Localization of SLNs is very important to this process. When preoperative imaging is done correctly it can be very useful in localizing the SLNs. However, performing preoperative imaging on some patients in some environments is difficult; thus, it is not performed on some patients for whom it might be appropriate. The use of intraoperative imaging in addition to intraoperative gamma counting might be a better approach to SLN localization than using only a gamma counting probe. The long-term objective of this project is determination of the feasibility and value of using a small field of view (FOV) gamma camera for intraoperative localization of SLNs in breast cancer patients who have not received preopertaive imaging .

BODY:

As an introduction and as part of the PI's educational training on SLN localization, the PI spent time analyzing data from melanoma studies that were being conducted at the Atlanta Veterans Affair Medical Center (VAMC) and Emory University. As a result of assisting with analysis of the data, the PI participated in and presented at Sentinel Node 2002, the 3rd International Sentinel Node Congress in Yokohama, Japan. The PowerPoint presentation is provided as appendix1. Attending the meeting was very informative and helpful educationally as regards the tasks of this research.

There is an existing database of one hundred and twenty-one breast cancer patients cared for between October 1998 and December 2000. The database was meticulously checked by the PI with the assistance of three other people to verify the validity of the contents of the database. Various statistical methods are being used to analyze the data. Correlations and differences between two different injection techniques for the radiotracers are being compared. A comparison of filtration size of the colloid is also being investigated in conjunction with other characteristics such as age, time to visualization, number of positive nodes by pathology, location of tumor and bra size. A summary/ publication is being written based upon the results of the analysis.

A clinical evaluation of a hand-held gamma camera with a pinhole aperture has been completed. Surgery and pathology information for 14 patients was collected and reviewed. Data were acquired from 14 surgery patients during preoperative imaging and during surgery. The full report "A clinical evaluation of a hand-held gamma camera", including images taken with the camera is included as appendix2. The small hand-held camera with the pinhole aperture was used to try and localize SLNs during preoperative imaging. Images of possible SLNs were acquired and recorded for 10 of the 14 patients.



The Fig. 1. (Left) Gamma Medica, INC., Northridge, CA, Hand-held Gamma Camera with pinhole aperture. (Right) Hand-held Gamma Camera with parallel-hole collimator.

Physicians uses of the hand-held camera were unable to locate possible SLNs in 4 of the 14 cases using the camera. The small camera used has a field of view of 1" x 1".

The camera uses a 14 x 14 array of NaI(Tl) scintillation crystals. Each crystal is 1mm x 1mm x 5mm; the crystals are separated by 0.25 mm of an optically opaque material. The scintillation crystals are coupled to a position sensitive photomultiplier tube The hand-held camera has a stainless steel handle, which acts as a housing unit for the wires and electronics. The hand-held device without the collimators weighs 0.74kg. Two types of collimators/apertures, as seen in figure 1, were evaluated. The pinhole aperture has a 3-mm diameter pinhole and a 30-mm focal length. The parallel hole collimator has a field of view that is the same as that of the scintillation crystal array. The pinhole aperture fit better on the prototype used for our investigation and therefore the pinhole aperture was used more than the parallel collimator. Users found it difficult to locate and image SLNs as they found the device to be heavy and cumbersome. It was difficult for the users to hold and direct. The users found the sensitivity of the pinhole aperture too low to conduct easily the task of SLN localization. The radiation shielding of the prototype was problematic, noise from the injection site often corrupted images of SLNs.

As a result of the difficulties with use of the 1" x 1" FOV hand-held camera with pinhole aperture, a larger FOV camera was acquired and is now being used in this project. The current camera has a 5" x 5" FOV. The FOV of the 5" x 5" camera is proving to be more appropriate for the task of SLN localization as specified for this project. The camera is heavy, greater than 14 pounds, and cannot be held by hand; therefore, it is attached to a surgical microscope support arm and mobile stand. The system also has a computer monitor and CPU. Fifteen breast surgeries have been completed. The first six cases were done using both the camera and probe in the operating room. The surgeon was not blinded to preoperative images acquired for every case. Nine cases have been conducted with the surgeon blinded to the preoperative images. The cases have been split between probe only and camera with probe studies. Data from the fifteen breast surgeries have been recorded and processed. The data have been transferred from the protocol instruments into a data file. Various quantitative data will be extracted and statistically analyzed.

As regards the status of the Tasks of the Statement of Work, the following summary is provided.

Task 1. Analysis of an existing breast cancer/sentinel lymph node (SLN) patient database.

The database (175+ patients) contains data of three sub-studies upon which we plan to report. To date, we have verified the contents (22 entries per patient) of the database for the 102 patients in the first sub-study and initiated verification of the database contents that for the second and third sub-studies. We have also initiated the statistical analysis of the data of the first sub-study. The task is not yet complete for two reasons: 1) The database contains more information than initially thought; and we have decided, as a result, to do a more extensive analysis than initially planned. and 2) The opportunity for more aggressive and substantial accumulation of data under Task 3 arose, and we have availed ourselves of that opportunity.

[Grant SF et al., 2002 is a preliminary report of data and analysis of the second sub-study. Preliminary reports of data and analysis of the first sub-study were reported before initiation of this project.]

Task 2. Characterization of small field-of-view (FOV) intraoperative gamma cameras.

Two small FOV gamma cameras have been used in the study. The first, the LumaGem Hand Held Probe (Gamma Medica, Inc., Northridge, CA) has a 1"x1" FOV. The second, the GammaCAM/OR (Gamma Medica, Inc., Northridge, CA) has a 5"x5" FOV. Preliminary data characterizing the devices and preliminary data obtained on 29 breast cancer patients and on 19 melanoma patients (separate funding) suggest for the task of SLN localization in the context of this project the 5"x5" FOV device is better than the 1"x1" FOV device. Thus, it has been decided that the 5"x5" FOV device will be used for the remaining effort of this project.

[Greene C, 2002, and Yamaguchi Y, et al., 2002, are summaries of experience to date with the 1"x1" device; Greene C, et al., 2002, Aarsvold JN, et al., 2002, and Aarsvold JN, et al., 2003, are summaries of experience to date with the 5"x5" device.]

Task 3. Acquisition of images/data from breast cancer patients using small FOV intraoperative gamma cameras.

Images/data for 14 Emory University breast cancer patients were acquired using the 1"x1" FOV device in the Nuclear Medicine Service at the Atlanta Veterans Affairs Medical Center (VAMC). Four nuclear medicine physicians were involved in this assessment stage. All concluded that this device was difficult to use for the task of SLN localization in breast cancer patients.

Images/data for 6 Emory University breast cancer patients were acquired using the 5"x5" FOV device in surgical suites at Emory University. Two oncology surgeons were involved in this assessment. Both concluded the device was acceptable for additional investigation. Based on this assessment, pursuit of data acquisition for the main objective of the study comparison of intraoperative SLN localization using a gamma counting probe and using a gamma counting probe and small FOV gamma camera-was initiated using the 5"x5" FOV device.

Images/data for 9 Emory University breast cancer patients have been acquired in the primary sub-study of this project. At least 11 additional patients will be enrolled in this sub-study.

[Greene C, 2002, Greene C, et al., 2003, Aarsvold JN, et al., 2002, and Aarsvold JN, et al., 2003, report aspects of this task and of similar tasks for SLN localization in melanoma patients.]

Task 4. Analysis of preliminary data of Task 3.

Aspects of the data of the 29 patients enrolled to date have been considered, summarized, and reported in Greene C, 2002, Aarsvold JN, et al., 2002, and Aarsvold JN, et al., 2003. Other aspects of the data of the 29 patients are of the same form as 50 patients of the existing database; consideration is being given to analysis of the similar components of the data of all 79 patients.

Task 5. Analysis of the data of the primary sub-study of Task 3.

Analysis of the data for the primary sub-study will be initiated when 11 additional patients have been enrolled and their core data acquired. It is anticipated that such analysis will be initiated between months 15 and 18 of the funding.

Task 6. Develop a PhD dissertation.

An independent project report has been submitted to the Georgia Institute of Technology (Greene C, 2002). Development of a PhD dissertation is on track to be completed as proposed.

KEY RESEARCH ACCOMPLISHMENTS:

- Verification of contents of an existing database and initiation of statistical analysis of the data.
- Investigation of 1" x 1" FOV hand-held gamma camera through acquisition of images/data of 14 patients.
- Acquisition and initial analysis of images of breast cancer patients in a sub-study to compare intraoperative SLN localization using only a gamma counting probe and SLN localization using a gamma counting probe and a 5" x 5" FOV gamma camera.

REPORTABLE OUTCOMES:

Yamaguchi, Yuko; MacDonald, Lawrence R.; Patt, Bradley E.; Iwanczyk, Jan S.; Aarsvold, John N.; Mintzer, Robert A.; Alazraki, Naomi P.; Greene, Carmen M. Evaluation of hand-held gamma camera with 1-mm NaI(Tl) pixels. SPIE ,Vol.4786, 9/2002.

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CONCLUSION

User experience suggests that for a 1" x 1" FOV hand-held device to have significant value in SLN localization, a user has to posses significant patience and be willing to progress through a steep learning curve. It has been concluded by the investigations on this project that several modifications of the prototype camera used would be necessary to investigate the device further. It has also been concluded that the FOV for a small device for SLN localization for breast cancer cases, especially cases without preoperative imaging should be larger than a 1" x 1". After a clinical evaluation of the device showed reason not to continue using such a small field of view, a 5" x 5" FOV system was acquired. Initial experience with the new system with a larger FOV camera suggests that it is more useful than the 1" x 1" hand-held camera. Anecdotal assessment of our use of the 5" x 5" FOV system suggests that use of camera and probe intraoperatively results in the surgeon having more confidence of localization and the removal of all radioactive nodes. Acquisition of the study data to support or refute this assessment is on-going.

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Appendix I

Sentinel Node 2002 Power Point Presentation:

Intraoperative Nuclear Medicine Imaging for Localization of Sentinel Nodes in Melanoma Patients

Intraoperative Nuclear Medicine Imaging for Localization of Sentinel Nodes in Melanoma Patients

C Greene[1], JN Aarsvold[2,3], RA Mintzer[2], SF Grant[3]
DR Murray[2], TM Styblo[2], RK Halkar[2,3], NP Alazraki[2,3]
LR MacDonald[4], JS Iwanczyk[4], BE Patt[4]

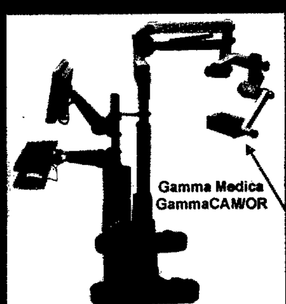
[1]*Georgia Institute of Technology, Atlanta, GA;*
[2]*Emory University, Atlanta, GA,*
[3]*Atlanta Veterans Affairs Medical Center, Atlanta, GA*
[4]*Gamma Medica Division, Photon Imaging Inc, Northridge, CA*

Long-term Objective

Development of SLN (sentinel lymph node) detection and localization protocols that include:

- intraoperative imaging with a small FOV (field-of-view) gamma camera
- intraoperative counting with a gamma counting probe

Small FOV Gamma Camera



pre- & post-excision imaging

56x56 array of 2x2 mm NaI(Tl) crystals
5x5 array of 1x1 in PSPMTs

Why intraoperative imaging?

- Present SLN protocols include
  1. preoperative imaging & intraoperative counting

  or

  2. intraoperative counting

The first is preferred and recommended. However, some institutions choose not to perform or are unable to perform preoperative imaging and some that do are unable to perform it with sufficiently high rates (~100%) of success.

- Alternative SLN protocols include
  3. intraoperative imaging & intraoperative counting

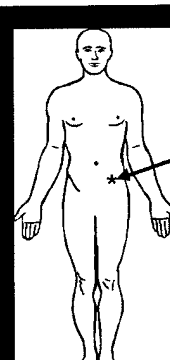
  or

  4. preoperative imaging & intraoperative imaging & intraoperative counting

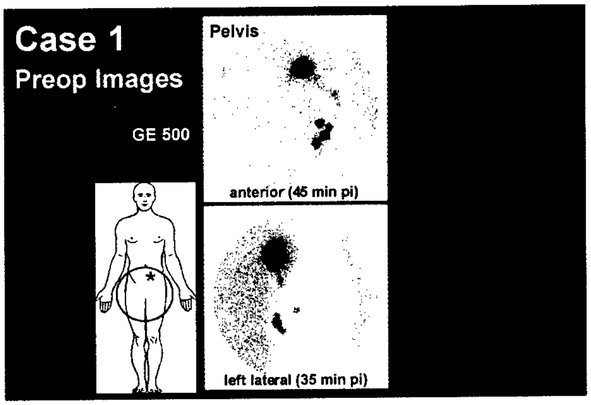
Methods

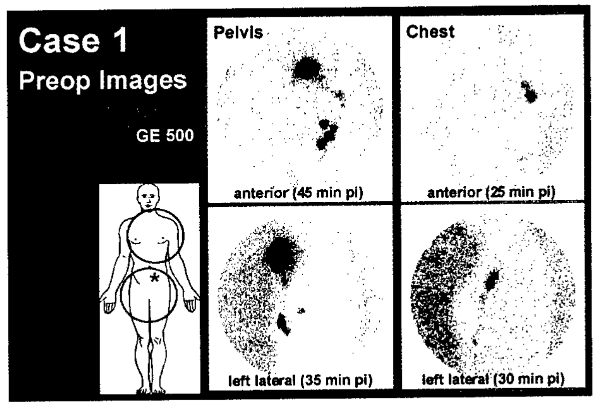
- *Subjects:* 3 F, 2 M, 42-72 yo, arm/abdomen/neck/trunk
- *Injections:* 2-4 intradermal, 0.2-0.3 cc/injection, 4.6-6.5 MBq (125-175 μCi) total, 0.22 μm filtered Tc^{99m} sulfur colloid
- *Preoperative Imaging:* GE 500, LEAP, dynamic & static
- *Intraoperative Counting:* Neoprobe 1000/1500
- *Intraoperative Imaging:* Gamma Medica GammaCAM/OR, pre & post excision
- *Specimen Imaging:* Gamma Medica GammaCAM/OR
- *Pathology:* IHC of SLNs, H&E of non-SLNs

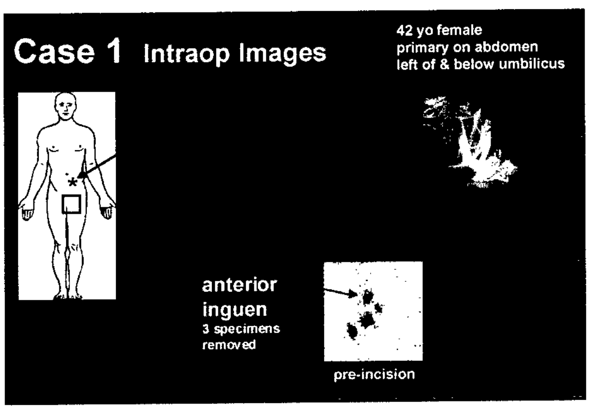
Case 1

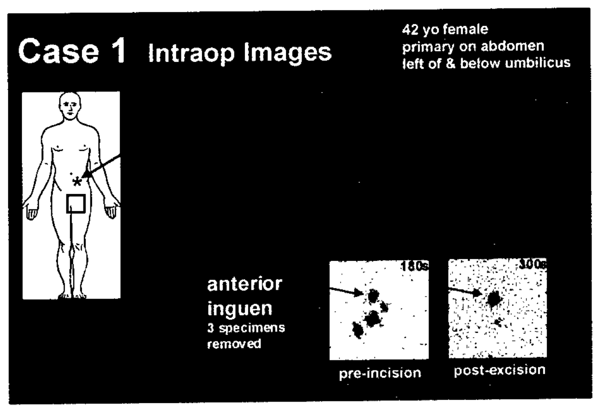


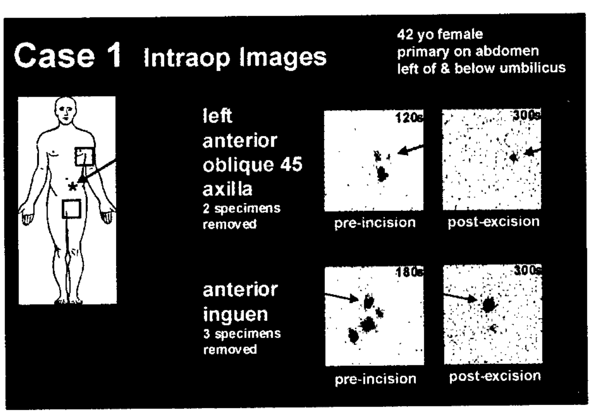
42 yo female
primary on abdomen
left of & below umbilicus

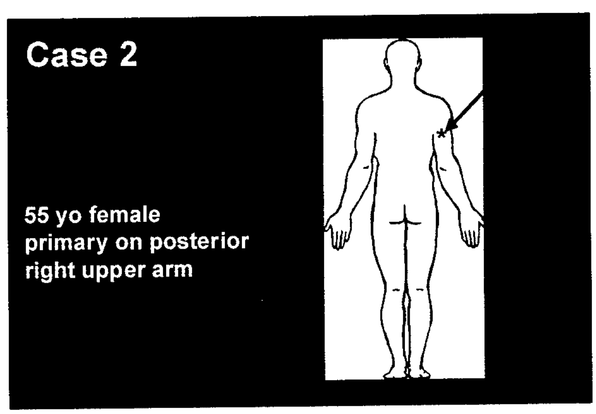

Case 1
Preop Images
GE 500
Pelvis
anterior (45 min pi)
left lateral (35 min pi)


Case 1
Preop Images
GE 500
Pelvis
anterior (45 min pi)
left lateral (35 min pi)
Chest
anterior (25 min pi)
left lateral (30 min pi)


Case 1 Intraop Images
42 yo female
primary on abdomen
left of & below umbilicus
anterior
inguen
3 specimens
removed
pre-incision

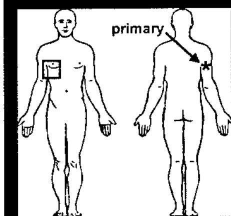

Case 1 Intraop Images
42 yo female
primary on abdomen
left of & below umbilicus
anterior
inguen
3 specimens
removed
180s
300s
pre-incision
post-excision


Case 1 Intraop Images
42 yo female
primary on abdomen
left of & below umbilicus
left
anterior
oblique 45
axilla
2 specimens
removed
120s
300s
pre-incision
post-excision
anterior
inguen
3 specimens
removed
180s
300s
pre-incision
post-excision

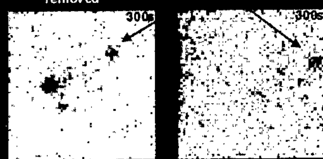

Case 2
55 yo female
primary on posterior
right upper arm

Case 2 Intraop Images

55 yo female
primary on posterior
right upper arm

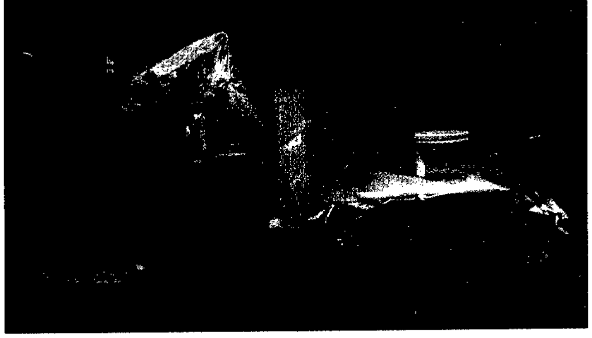


right
anterior
oblique 30
axilla
4 specimens
removed

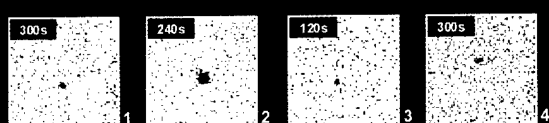


pre-incision post-excision

Specimen Imaging



Case 2 Specimen Images



Specimen ID	post-ex cts (10s) (probe)	post-ex cts (net) (camera)	activity (nCi)	specimen/injected activity (%)
1(nonSLNax)	0	49	73	0.09
2(SLNax)	5921	613	1134	1.39
3(SLNax)	548	12	45	0.06
4(SLNax)	423	27	40	0.05

Observations

Camera Design

1. sensitivity more important than resolution
2. positionability & repositionability important
3. low, uniform noise important
   [every focus on an image should represent a true accumulation of activity]
4. field of view --large enough that regional surveys can be completed in reasonable times
   --small enough that positioning is easy

Camera Value

An intraoperative camera makes possible

1. quick and accurate surveys of relevant nodal basins
2. accurate assessment of residual activities in excision beds
3. accurate assessment of activities in excised tissues

Active Efforts

Our present efforts include studies to compare intraoperative use of probe and camera with intraoperative use of probe only.

The efforts include studies involving melanoma and breast cancer patients.

This work supported in part by
NIH grant NCRR #2R44RR15157.

Appendix II
Paper Submitted to Georgia Institute of Technology:

A Clinical Evaluation of a Hand-held Camera

Clinical Evaluation of a Hand-held Gamma Camera

Carmen Greene

Abstract

Staging is very important as regards prognosis and management of breast cancer patients. One method of staging is analysis of sentinel lymph nodes (SLNs). Several techniques exist for the localization, excision, and analysis of SLNs. Those that include high quality preoperative imaging, careful intraoperative gamma counting, and detailed pathology analysis generally produce data that lead to accurate staging and appropriate management. Some institutions, however, choose not to perform preoperative imaging and some that choose to are unable to perform high quality imaging. As a result, staging and therapy plans for some patients are not as accurate and appropriate as they might be. Two alternative techniques that have been proposed are one that includes preoperative imaging with a conventional gamma camera, intraoperative imaging with a novel small field-of-view (FOV) imager, and intraoperative gamma counting with a gamma counting probe, and one that includes intraoperative imaging and intraoperative gamma counting. Here, we report results of a short preliminary study conducted to investigate the use of a novel hand-held gamma camera (HHC) (Gamma Medica, Northridge, CA) for intraoperative imaging. The device investigated comprises a 14x14 array of NaI(Tl) scintillation crystals and a 1-in x 1-in position sensitive photomultiplier tube (PSPMT); the device's intrinsic FOV is 2 cm x 2 cm. Fourteen breast cancer patients scheduled for surgery involving SLN analysis were enrolled in the study. Each received standard management, including standard preoperative imaging, intraoperative counting, surgery, and pathology analysis. In addition, each patient was imaged by one or more nuclear medicine physicians, residents, engineers, or technologists using the HHC. Acquired images were generally 30-sec images. As this study involved the first clinical use of the HHC for SLN localization, the imaging was done preoperatively in the nuclear medicine clinic rather than intraoperatively and was primarily a familiarization exercise for eight potential users. Imaging sessions of ten- to forty-minutes duration were conducted for each subject with sample images recorded for 10 of the subjects. Only a few of the imaging sessions were deemed by users to be reasonably successful. The users felt that the device was difficult to use for the specified task. It is concluded that a device with a FOV such as that on the HHC will not prove useful for the task of SLN localization in breast cancer patients.

Introduction

Staging of cancers is an important factor in determining a patient's prognosis. For breast cancer patients, staging involves assessment of relevant lymph nodes including, but not limited to, axillary lymph nodes. Full axillary lymph node dissection (FALD), the removal of most axillary nodes has been for many years the standard of care for the staging of breast cancer patients. Removal and histological analysis of tens of nodes is common in such procedures. The technique generally works but has a couple significant problems. One, axillary node dissection can result in significant morbidity such as lymphodema. Two, histological analysis of the nodes is limited, as the shear number of nodes resected restricts practically the time that can be committed to the analysis. The lack of a thorough investigation of the nodes increases the chances that a metastasis is missed and a false negative result occurs. For 20% - 40% of early breast cancer patients (tumor size, less than or equal 2 cm), a FALD results in a negative axilla. But, a negative axilla at this examination does not give any information (Guiliano Mariani). Unfortunately, for these patients, many will experience the adverse side effects of a FALD without the gain of useful information. An alternative method to removing all axillary lymph nodes is the removal of a few key nodes. Removing a few key nodes is the method of SLN resection. The idea of SLN is that lymph flow follows an orderly process, and because it does, occurance of metastases will be systematic as well. That is, if the key nodes, the SLNs, are not metastatic, then none of the other nodes are metastatic and only the SLNs need be assessed. Thus, SLN procedures are designed to locate SLNs and have them analyzed. As there are generally only a few SLNs, the histological analysis performed on each can be and is much more extensive then that done on nodes excised in a FALD.

Currently, there are several procedures used to perform SLN resection. They do not all have the same success rate. One technique involves the injection of a radiotracer into a patient followed by the acquisition of a lymphoscintigraphy. A counting probe is used during surgery to assist in the localization of the nodes and to check for residual activity after the SLNs have been removed. A procedure is considered successful if SLNs are identified, removed, and assessed. Preoperative imaging is an important component of a SLN procedure in which radioactivity is used. But, it is not performed or not performed well at many institutions. The reasons for this are many. An alternative method to preoperative imaging is intraoperative imaging. Intraoperative imaging could provide much of the information that preoperative imaging can and may also be done more practically at some institutions. Several devices with FOVs of various sizes (2cm x 2cm to 20 cm x 20 cm) have been proposed for the task of intraoperative imaging. Here is reported a preliminary investigation of such a device with a 2 cm x 2 cm FOV (Hand-Held Gamma Camera from Gamma Medica, Northridge, CA).

Sentinel Lymph Node Techniques

Penile cancer was the first clinical setting in which sentinel node biopsy was performed; this was reported by Cabanas in 1976 [a]. In this report he showed evidence of lymphatic drainage from the tumor bed to nodes. Presently there are two main categories of techniques used for locating sentinel nodes. The first technique uses a patent blue dye to map the sentinel nodes. The blue dye is injected in or around a tumor and its migration and accumulation is visualized within the lymphatics. The blue dye stains lymph nodes and channels. The second technique uses a radiocolloid and a gamma-detecting probe. The radiocolloid is injected into the patient anywhere from twenty-four hours to a few hours before surgery. An appropriate radiocolloid has two main properties. One, it is quickly taken up by nodes, and two, it has an affinity for and a high retention in lymph nodes [b]. There are a few ^{99m}Tc labeled colloids that are licensed for lymphoscintigraphy (Table 1).

Table 1
Radiopharmaceuticals Used in Sentinel Node Procedures

Radiopharmaceuticals	Place licensed	Average particle size
^{99m}Tc sulfur colloid (SC)	United States	100-500 nm/ filtered
^{99m}Tc antimony trisulfide colloid (ATC)	Europe	3-30nm/ unfiltered
^{99m}Tc nanocolloidal albumin (CA)	Europe	5-80nm/ unfiltered

The radiocolloids can be injected a number of different ways: intradermally, subdermally, intratumerally, or peritumerally. After the radioisotope is administered, the lymphoscintigrapy is performed. Sometimes the breast is massaged for 2-5 minutes after the tracer is injected; this is done to promote the migration of the tracer from the injection site to nodes. Initiation of imaging varies from institution to institution. At some institutions, it commences immediately; at others it commences one to three hours post injection. Images may take less then 30 minutes or may continue for several hours. Most nodes are visualized within thirty minutes. Some factors that should be considered for preoperative imaging are patient positioning on the imaging table, positioning of the breast so the injection site does not cover the area of interest, acquisition from various views, and acquisition of anatomical references as regards the nodes. When done correctly, preoperative imaging provides all the essential information needed for a successful SLN localization.

The conventional gamma camera typically has a field of view of 400mm by 500mm[c]. This FOV is large enough to give the surgeon a full perspective of the location of the nodes. Often for anatomical reference, a transmission source, a ^{57}Co or ^{99m}Tc flood source, or flexible line source is used to define a patient's body contour. The conventional gamma camera consists of a collimator in front of a scintillation crystal coupled to an array of photomultiplier tubes. The collimator is a honeycomb structure that acts as a filter for scattered gamma rays; most gamma rays traveling towards the detector, but not on a path perpendicular to it, are absorbed by the collimator. Imaging of breast patients is normally done using a low-energy high-resolution (LEHR) or a low-energy all-purpose (LEAP) collimator.

The conventional method for SLN resection makes use of a gamma counting probe. Most hand held gamma probes are solid state detectors. A filtered-radioisotope-tagged colloid, such as ^{99m}Tc sulfur colloid, is injected into the patient hours before surgery. During the surgery, the gamma counting probe is used to map the SLNs. The lymph nodes are mapped by the detection of the gamma rays being emitted from the radioisotope. The earliest probes were used for eye tumors and detected P-32.

Gamma Counting Probes

Gamma counting probes are relatively light weight. The main characteristics of a probe that are important in this context are spatial resolution, sensitivity, count rate linearity, and shielding [f]. As stated above, each intraoperative probe has either a scintillation detector or an ionization detector [e]. Ionization detectors read electrical pulses that are made from the free electrons that are produced from ionizing radiation [e]. Just as in a large gamma detector, there is an energy peak window, for example 140keV ± 10%-20%. The window is a filter of the radiation detected. Sensitivity of a gamma probe is the count rate per unit activity; this can also be called efficiency. Sensitivity is hard to measure since it is geometrically dependant [g][f][e]. Spatial resolution of a gamma probe refers to its ability to accurately determine the location of a signal. Shielding is very important because an injection site can be very close to a SLN being sought and thus very close to the probe being used in a search. Shielding generally goes over the handle of the probe, but it is usually the least amount needed so that shielding is sufficient yet the probe is light enough to be comfortable to hold. The collimator over the face of the detector also acts as a shield.

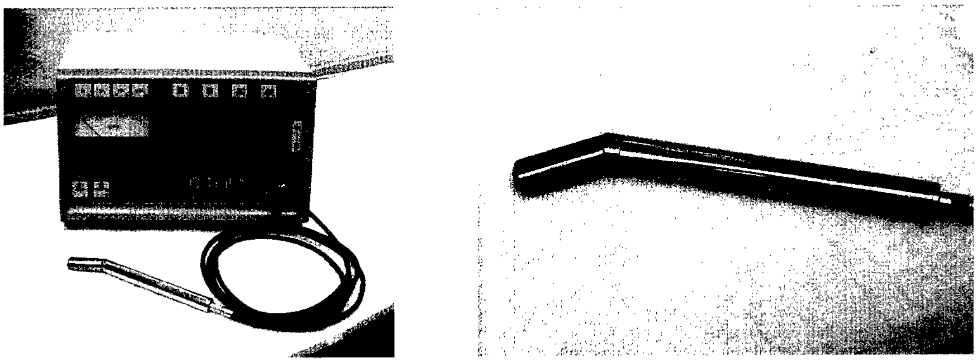


Fig. 1 (Left) C-Trak gamma counting probe system. (Right) Close-up of the detector (the probe).

Surgery

There are two categories of methods for intraoperative sentinel node mapping, a blue dye category and a radioguided category. Some surgeons choose to use blue dye only. These surgeons inject 1-5ml of the blue dye, at the start of surgery. The surgeon then usually massages the breast and makes an incision in the axillary region. The stained lymph channels and nodes are visualized and the nodes resected [d]. Other surgeons use radiolabeled colloid. If the patient had a lymphoscintigraphy, there is no need for another injection of the radiocolloid. The surgeon spends the first few minutes of surgery searching for the node with the probe. The radiation in a node is detected prior to the making of an incision. Using the probe, the surgeon usually is able to locate the nodes to be excised before making an incision. The probe that is used during surgery is covered with a sterile sheath because it is used in the sterile surgical field.

Fig. 2. Surgeon with a gamma counting probe sheathed for use in the sterile field.

After the incision is made, the probe is positioned against the lymph node, inside the excision bed, to ensure the surgeon has located the node of interest. After the specimen is removed from the patient, the probe is placed back into the excision bed to see if there is any activity remaining. Lymphoscintigraphy adds to the surgeon's confidence and can help reduce the time to search for nodes [d]. Some surgeons use a combination of the two techniques, blue dye and radiocolloid, including use of preoperative imaging. When the techniques are performed correctly, groups that use a combination method generally have a high success rate regarding localization of SLNs [d][c].

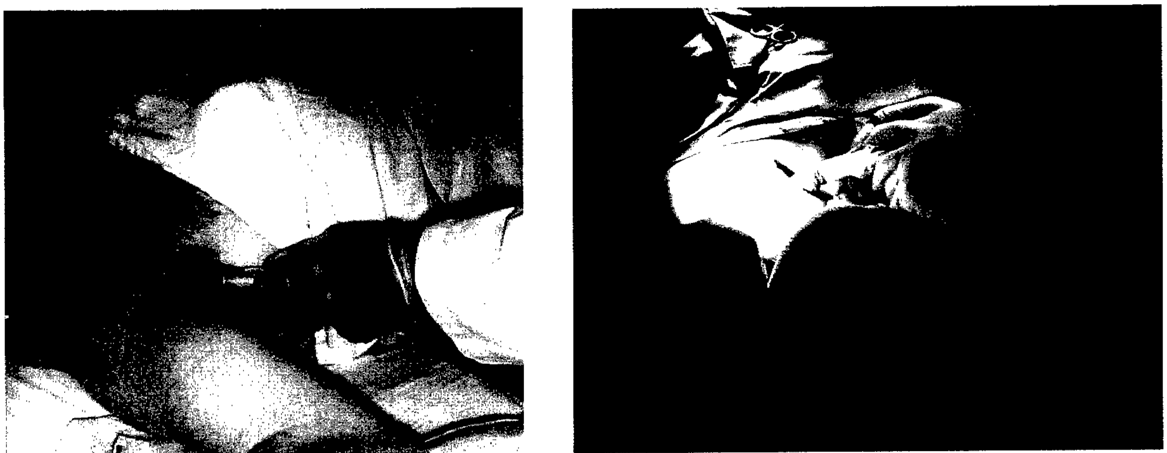


Fig. 3. (Left) Surgeon using gamma counting probe pre-incision to locate axillary accumulations (likely in lymph nodes) of radiotracer. (Right) Surgeon using gamma counting probe post-incision to locate lymph nodes that are radioactive.

Methods and Materials

Data from fourteen subjects were acquired for this preliminary characterization of a hand-held gamma camera in the task of SLN localization in breast cancer patients. The fourteen subjects were consented and enrolled per a protocol approved by the internal review board of Emory University and the Atlanta Veterans Affairs Medical Center (VAMC—Atlanta). The study was conducted at the VAMC—Atlanta and Emory University. Subject management was consistent with that which each patient would have received if they were not in the study. The procedures for the patients included injections of a radiolabeled colloid, preoperative imaging with a conventional gamma camera, intraoperative injection of blue dye, intraoperative gamma counting, resection of SLNs, a complete pathology report, and follow-up care. In addition, the subjects were imaged preoperatively with the hand-held gamma camera positioned by one or more nuclear medicine physicians, residents, technologists, or engineers.

Gamma Medica Hand-held Camera

The hand-held camera (HHC) used in this study was designed specifically for nuclear medicine applications [i]. The camera is designed with the same functions as those found on a gamma counting probe. It also has a visual output for display of detected gamma radiation. It is very important for some surgeons that there is an audible indicator of the detected radiation. The HHC has audio output and is such that the user can turn the sound off and on. The HHC is a small gamma camera. It has a field of view that is 2 cm x 2 cm. An earlier prototype had an array of 16 x 16 CsI(Na) crystals. The prototype that was used in these investigations has an array of 14 x 14 NaI(Tl) scintillation crystals. The dimensions of each crystal are 1mm x 1mm x 5mm. The crystals are separated by 0.25 mm thick optically opaque material. The scintillation crystals are coupled to a position sensitive photomultiplier tubes (PSPMT) with an optical coupling agent. The HHC has a stainless steel handle, which acts as a housing unit for the wires and electronics connected to the HHC. The weight of the HHC without a collimator is 0.74 kg. There are different types of collimators and apertures for the HHC, but the two of interest for this study were a parallel-hole collimator and the pinhole aperture. The pinhole aperture has a 3-mm diameter pinhole and is 30 mm long. It is made of lead and has a thickness of 3.4 mm. The collimator alone weighs 0.27 kg. The pinhole aperture is likely to be more frequently used in breast SLN identification than and other collimator or aperture because its variable magnification provides greater flexibility for viewing than others. The FOV of the parallel-hole collimator matches that of the scintillation crystal array. The processing and acquisition electronics of the HHC allows real-time imaging with an audible count-rate. The system also has a foot switch that allows the operator to start and stop acquisitions while holding the device.

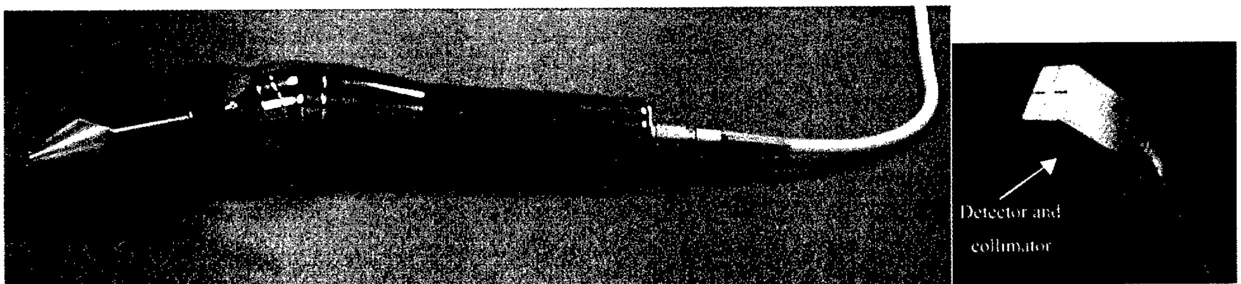


Fig. 4. (Left) Gamma Medica Hand-held Gamma Camera with pinhole aperture. (Right) Hand-held Gamma Camera with parallel-hole collimator.

Subjects

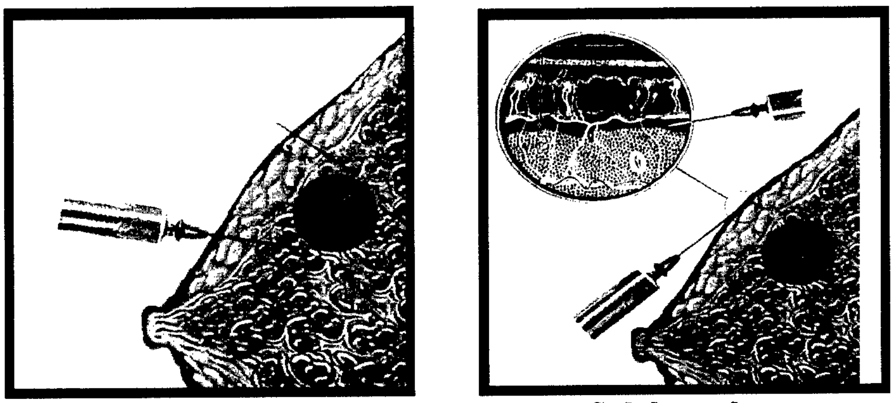
The subjects for the study were fourteen consecutive patients scheduled for breast cancer surgery that included SLN procedure. A summary of some characteristics of the subjects and their disease types are given in Table 2. The disease types were infiltrating ductal carcinoma (IDC), infiltrating lobular carcinoma (ILC), and ductal carcinoma in-situ (DCIS).

Table 2
Subject Characterization

Subject	Sex	Age	Cup size	HHC collimator	Disease location	Disease type
1	F	60	B	Pinhole	Left @ 12 & 3	IDC
2	F	34	D	Pinhole	Right @ 3:00	IDC
3	F	46	B	Pinhole	Right @ 6:30	ILC
4	F	44	D	Pinhole	Right @ 9:00	IDC
5	F	58	C	Pinhole	Right @ 11:00	ILC
6	F	53	B	Pinhole	Right @ 5:30	IDC
7	F	52	B	Pinhole	Right @ 9:00	IDC
8	F	54	B	Pinhole	Right @ 12:00	DCIS
9	F	41	B	Pinhole	Left @ 2:00	IDC
10	F	58	B	Parallel-hole	Right @ 12:00	ILC
11	F	53	D	Pinhole	Right @ 2:00	C
12	F	67	A	Pinhole	Left @ 9:00	IDC
13	F	42	C	Pinhole	Right @ 10:00	DCIS
14	F	56	B	Pinhole	Left @ 12:00	IDC

Radiopharmaceutical Injection

On the day of surgery each subject was prepared for the preoperative imaging. The subjects lay down on the imaging table and were positioned by a nuclear medicine technologist. Each subject received three injections of 0.22-μm filtered ^{99m}Tc sulfur colloid. Two of the injections were peritumoral and consisted of approximately 125 μCi in 1 ml. The third injection was subdermal and consisted of approximately 250 μCi in 0.3 ml. Prior to the injections, all three syringes were shaken to ensure the colloid was suspended in solution and well mixed. The breast was massaged for one to five minutes after the third injection, to facilitate the flow of the radiopharmaceutical away from the injection site and into the lymphatic system.



Peritumoral **Subdermal**

Fig. 5. (Left) Schematic of peritumoral injections. (Right) Schematic of subdermal injection. Schematics were adapted from Keshtgar MRS, Waddington WA, Lakhani SR and Ell PJ. *The Sentinel Node in Surgical Oncology*, Berlin: Springer-Verlag, 1999, pp 51, 54.

Preoperative Imaging

A conventional single-head gamma camera, a GE 500, was used to do preoperative imaging of the subjects. Immediately following the massaging of the breast, the image acquisition was started. The first set of images acquired recorded the dynamic flow of the radiotracer through the lymphatic channels and nodes. These images helped identify the order in which the nodes were visualized, which helps identity sentinel nodes from secondary nodes. The first sets of images were taken in frames with time intervals from three to ten minutes. The images acquired included anterior, lateral, and oblique views. Viewing of all three projections, results in a greater understanding of the positions of the nodes. A cobalt-57 source was placed on the opposite side of the subject from the camera to obtain an outline of the subject in the image. The outline provided an anatomical reference for localization of the sentinel nodes. After the nodes were localized marks were placed anteriorly and laterally on the subject using a surgical marker. These marks provided the surgeon a guide as to where to initiate her search for SLNs.

After the images were acquired using the conventional gamma camera, images were acquired using the HHC. For subjects that had the additional preoperative imaging done with the hand-held gamma camera invisible ink was used to mark the subjects instead of the surgical marker. The invisible ink was used to blind the user to knowledge of the node. After the invisible mark was made on subject, the user spent ten to forty minutes seeking SLNs. A nuclear medicine technologist and/or engineer assisted in the operation of the HHC during each session.

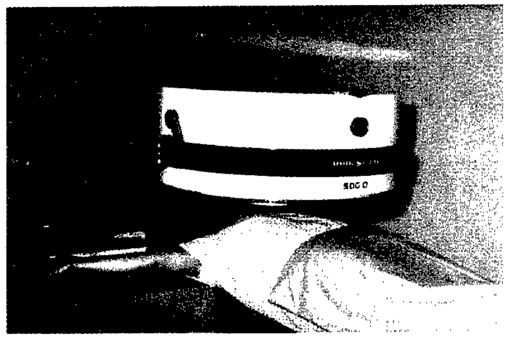


Fig. 6. A conventional gamma camera (a General Electric 500 gamma camera).

Blue Dye Injection

Subjects were scheduled for surgery from two to eighteen hours after completion of the preoperative imaging. In the surgical suite after the subjects received anesthesia, they were given injections of isosulfan blue dye. This dye migrates into the lymphatic system and provides a possible means of visually identifying SLNs. Three to five injections with a total volume of 5 cc were given. After the dye was administered, the surgeon massaged the breast for one to five minutes.

Intraoperative Counting

After the blue dye was administered, the surgeon used the gamma counting probe to localize sentinel nodes. The counting probe, a Carewise C-Trak, was covered with a sterile sheath (Figs. 1-2). The surgeon used the preoperative images and the marks on the subject's skin for reference. Once the surgeon was confident she had located the area of interest, she made an incision. The counting probe was inserted into the incision and used to locate the node. After localizing the node, the surgeon removed the node and counted the excised tissue ex-vivo. The ex-vivo count was a ten second acquisition done with the probe directed at the specimen such that the count rate was maximized. A second acquisition of counts, one of activity in the excision bed, was also performed. Some specimens were sent to pathology for frozen-section analysis. Before completion of the surgery, a report from pathology was given to the surgeon. The surgeon then completed the surgery with the removal of more axillary nodes, the removal of more tissue, or the closing of the subject's incision.

Pathology

Some of the specimens that were excised during surgery were sent to pathology for immediate testing for metastases. Specimens tested during surgery were frozen sectioned, haematoxylin and eosin (H&E) stained, and analyzed for metastases. Results of this procedure are sent immediately to the operating room as they can sometimes affect the surgical procedure. The lymph nodes were examined within thirty minutes of resection. The specimen were sliced in two and then frozen using a cryo-spray. The halves were then cut into three pieces and H&E stained. If the frozen section is positive, the patient is labeled positive for metastasis. This may lead to additional surgery and/or to additional adjuvant therapy. If the frozen section is negative, further testing is done later on each excised node, particularly those labeled as SLNs. The additional testing usually involves imunohistochemistry (IHC) analysis. The IHC analysis uses a pan-cytokeratin antibody to detect micrometastases and is done on numerous slices of each node, more than on the number of slices used at the time of frozen section analysis.

Results

Imaging sessions involving the use of the HHC were conducted on 14 subjects. Each session generally involved at least two users of the HHC. For some sessions, the users had access to the preoperative images acquired with the conventional gamma camera and for others they did not. In some sessions, both users participated simultaneously; in others, the users participated sequentially. These variations were the result of practical issues of user availabilities rather than study or systematic considerations. The appendix to this document includes a summary of study data that includes most of the images acquired and stored for the study subjects. The appendix includes conventional gamma camera images, hand-held camera images, a summary of the pathology of the excised nodes, and some comments and observations about each case. Most of the acquired images are unimpressive. The imaging sessions for subjects 6, 7, 9, and 11 were the most successful in that at least one user in each of those sessions was able to acquire some images of relevant foci of activity. Most sessions were not very successful. Users found the device heavy and thus difficult to hold and direct. Users found the sensitivity of the pinhole aperture too low to conduct easily the task of SLN localization. Users found that the learning curve for effective use of the system was steep, in part, because they found it difficult to get accustomed to the variations in magnification that result as the pinhole aperture is positioned at various distances from a subject.

Conclusions

The HHC might have value for SLN localization in the hands of a user with patience willing to progress through a steep learning curve as regards use of the HHC. The primary users in this study indicated that the learning curve appeared to be too steep for the value of even the optimal outcome of expected use. The study to test this HHC prototype was, as a result, terminated.

The primary complaints of the users were the limited sensitivity of the system and the moderately complicated positioning process necessary to successfully obtain an image of tracer accumulation using a pinhole aperture and the small FOV detector. The users also complained of what seemed to be minimal shielding. The shielding on the hand-held camera had an effect on the difficulty of interpreting the images. The shielding seemed inadequate. Scatter appeared in some of the images and confused the users who were subsequently unable to determine exactly what was revealed in the images. The small FOV left the users without an anatomical reference when a focus was revealed in the image, often leaving the users confused as to where they were imaging.

The HHC device may find use in some setting, but the conclusion of the participants of this short study was that it would not likely be useful for the task of SLN localization in breast cancer patients. The participants further concluded that the device was fairly representative of such small devices and speculated that most other devices with similar small FOVs (< 5 cm x < 5 cm) would likely prove to have just as steep a learning curve. The participants concluded that further studies on intraoperative SLN localization in breast cancer patients should be performed using devices with FOVs at least 12 cm x 12 cm.

References

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Appendix 1

This appendix contains a summary of the data acquired for this study. It includes conventional gamma camera images, hand-held camera images, a summary of the pathology of the excised nodes, and some comments and observations about the studies performed on each subject. Conventional gamma camera images include anterior, lateral anterior-oblique and lateral. The images have a acquisition time of 2 to 5 minutes. Hand-held system images are displayed two ways, as raw 14 pixel x 14 pixel data and below the raw data smoothed. The hand-held images also have the total number of counts and the image duration. The pathology summary tables include the following information: sample identification number as designated in surgery; indicators observed during surgery (presence or absence in the sample of radioactivity and/or blue dye); number of counts obtained in 10 seconds with the gamma counting probe; number of metastatically positive nodes out of total number of nodes in a sample (as determined by frozen section pathology); number of metatastically positive nodes out of total number of nodes in a sample (as determined by immunohistochemical analysis).

Subject 1

Subject is a 60 year-old-female with infiltrating ductal carcinoma located at 3:00 in her left breast. The preoperative images taken with the LFOV conventional gamma camera are shown in Fig. S1-C. The preoperative hand-held images are shown in Fig. S1-H.

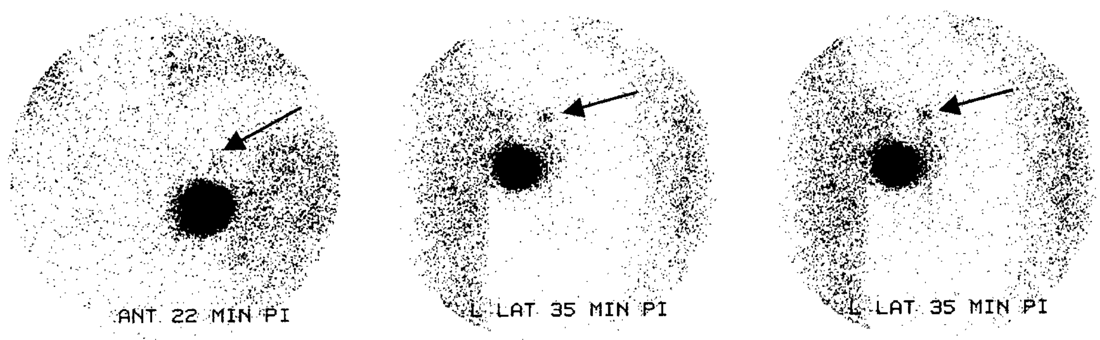
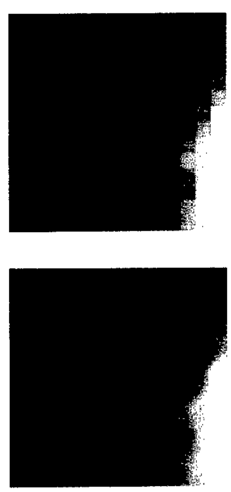


Fig. S1-C. Preoperative images acquired with conventional gamma camera. In each picture the injection site is visible. (L to R) Axillary focus is visible on all views, although it is not clear in the anterior view.



Counts: 79,088
Time: 120 sec

Fig. S1-H. Preoperative image of the injection site off to the right of the hand-held camera.

Table S1

Sample ID	Indicators	Post-ex count	Frozen sect.	IHC
1	blue/hot	1728	NA	1/1
2	blue/hot	799	0/4	0/4

Intraoperative data and pathology results for excised tissue samples.

Subject 2

Subject 2 is a 34 year-old female with infiltrating ductal carcinoma located at 3:00 on the right breast. No preoperative images were recorded using the hand-held. The preoperative images acquired using the LFOV conventional gamma camera are shown in Fig. S2-C.

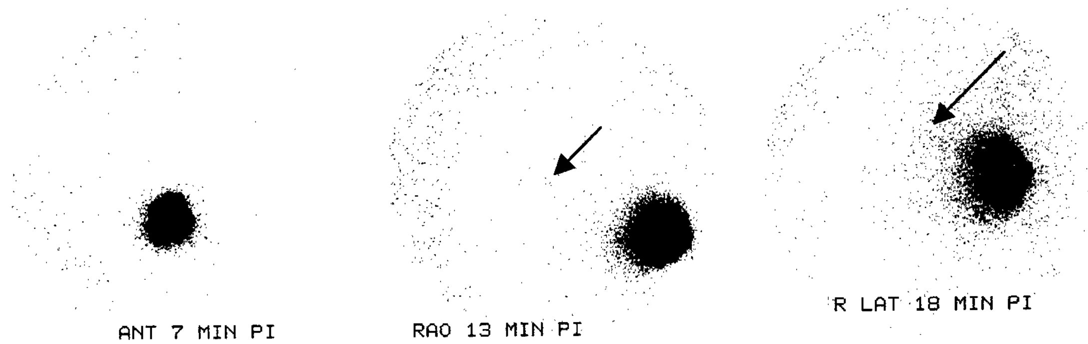


Fig. S2-C. Preoperative images taken with the conventional LFOV gamma camera. All of the imags show the injection site. Anterior view does not clearly reveal a focus. Right anterior oblique view does not clearly show reveal axillary focus. Right lateral view does not show focus as clearly.

Table S2

Sample ID	Indicators	Post-ex count	Frozen sect.	IHC
1	Blue/hot	571	0/1	0/1
2	Not blue/hot	111	0/1	0/1
3	Not blue/hot	131	0/1	0/1

Intraoperative data and pathology results for excised tissue samples.

Comments
No preoperative images were recorded using the hand-held. The nuclear medicine residents and physicians practiced handling the camera and getting adjusted to using the camera with a patient.

Subject 3

Subject 3 is a 46 year-old female with infiltrating lobular carcinoma located at 6:30 in the right breast. The preoperative images acquired using the LFOV conventional gamma camera are shown in Fig. S3-C.

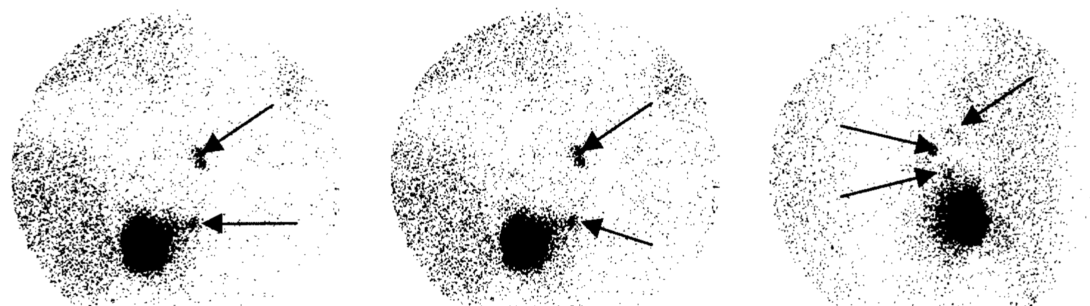


Fig. S3-C. Preoperative images taken with the conventional LFOV gamma camera. All of the imags show the injection site. Anterior view most clearly reveals 3 intermammory foci and associated channels. Axillary foci are seen on the right anterior oblique and right lateral views.

Table S3

Sample ID	Indicators	Post-ex count	Frozen sect.	IHC
1	Blue/hot	1705	0/2	0/2
2	Blue/hot	619	0/1	0/1
3	Blue/hot	865	0/1	0/1
4	Blue/hot	659	0/2	0/2

Intraoperative data and pathology results for excised tissue samples.

Comments
The residents and the physicians to used this trial to get acclimated to the hand-held camera. Therefore no preoperative hand-held images were taken of this patient

Subject 4

Subject 4 is a 44 year-old female with infiltrating ductal carcinoma located at 9:00 in the right breast. The preoperative images acquired using the LFOV conventional gamma camera are shown in Fig. S4-C.

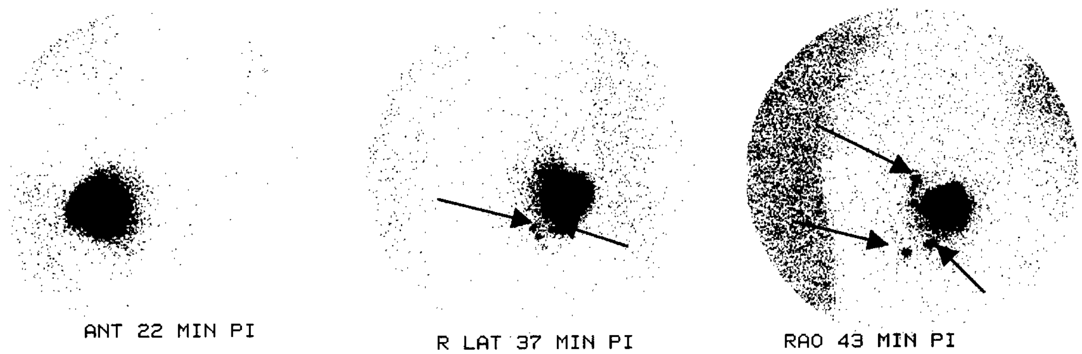


Fig. S4-C. Preoperative images taken with the conventionl LFOV gamma camera. All of the images show the injection site. Anterior view does not clearly reveal a focus. Right lateral view reveals multiple lateral nodes. The right lateral oblique view also reveals axillary foci.

Table S4

<table>
<tr><th>Sample ID</th><th>Indicators</th><th>Post-ex count</th><th>Frozen sect.</th><th>IHC</th></tr>
<tr><td>1</td><td>Blue/hot</td><td>2721</td><td>0/1</td><td>0/1</td></tr>
<tr><td>2</td><td>Blue/not hot</td><td>X</td><td>NA</td><td rowspan="2">0/3</td></tr>
<tr><td>3</td><td>Blue/not hot</td><td>X</td><td>NA</td></tr>
</table>

Intraoperative data and pathology results for excised tissue samples.

Comment

The subject does not have any preoperative images acquired by the hand-held imager. The residents and physicians were getting acclimated to the camera with the assistance of subject 4.

Subject 5

Subject 5 is a 58 year-old female with infiltrating lobular carcinoma located at 11:00 in the right breast. The preoperative images taken with the conventional LFOV gamma camera are shown in Fig. S5-C. Three images were taken using the hand-held camera and are shown in Fig. S5-H.

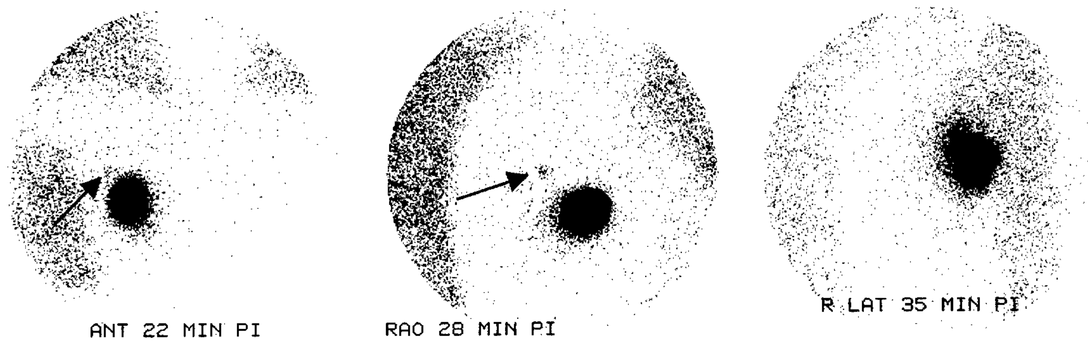
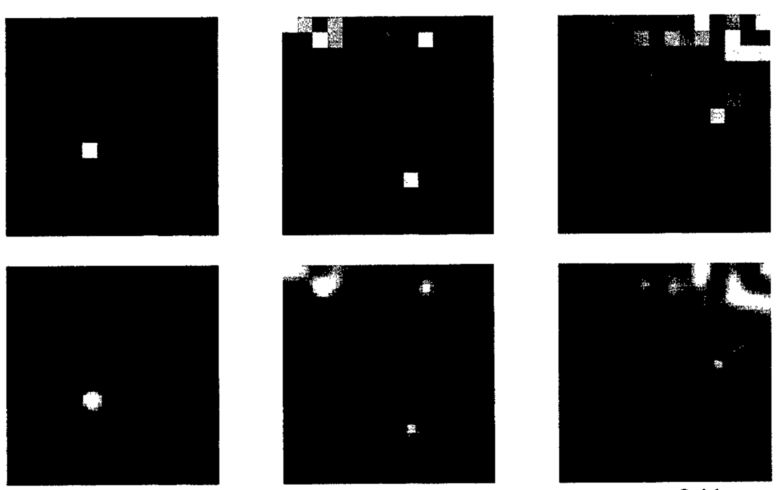


Fig. S5-C. Preoperative images taken with the conventional LFOV gamma camera. All of the images show the injection site. The anterior view reveals an axillary focus. The right anterior oblique view also reveals at least on focus. The right lateral view does not show focus clearly.



Counts:	127	81	241
time:	30 sec	30 sec	30 sec

Fig. S-5H. These preoperative images were taken with the hand-held camera. The top images represent the 14-pixel x 14-pixel raw data and the bottom images are smoothed. (L to R) The first image shows a focus but the injection site is not within the FOV. The next image shows evidence of some activity in upper right hand corner. The third image shows evidence in the axillary of activity from a node.

Table S5

Sample ID	Indicators	Post-ex count	Frozen section	IHC
1	blue/hot	3787	0/1	0/1
2	blue/hot	1433	0/1	0/1

Intraoperative data and pathology results for excised tissue samples.

Subject 6

Subject 6 is a 53-year-old female with infiltrating ductal carcinoma located at 5:30 in the right breast. The preoperative images taken with the LFOV conventional gamma camera are shown in Fig. S6-C. Preoperative images were taken with the hand-held camera are shown in Fig. S6-H.

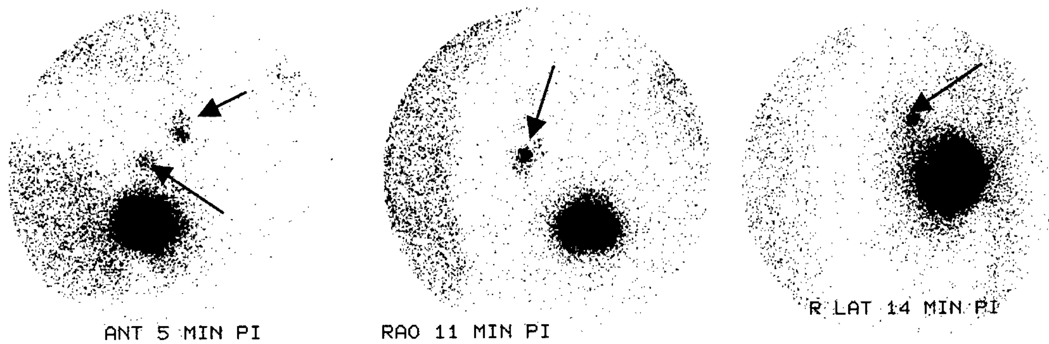
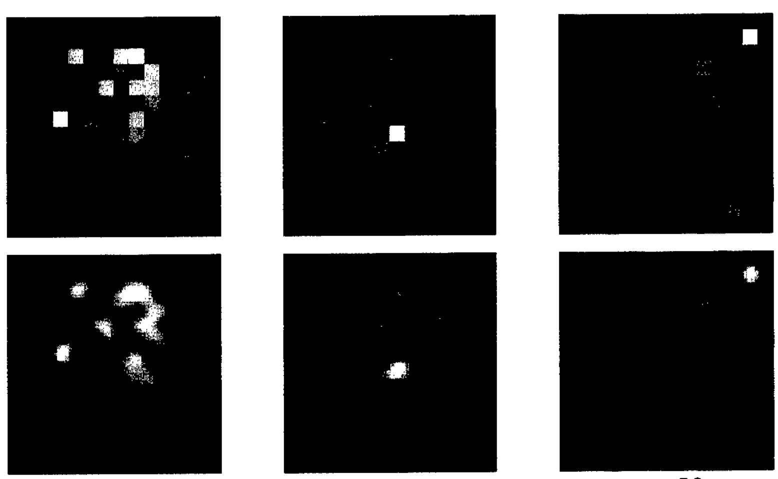


Fig S6-C. Preoperative pictures taken with conventional gamma camera. (L to R) All of the images show the injection site. Anterior view shows axillary and subclavian foci above the injection site. Right anterior-oblique view and lateral views show only an axillary clearly.



Counts:	283	270	59
Time:	30 sec	30 sec	26 sec

Fig. S6-H. These preoperative images were taken with the hand-held camera. The top images represent the 14-pixel x 14-pixel raw data and the bottom images are smoothed. (L to R) The first image shows a focus but the injection site is not within the FOV. The next image shows evidence of some activity in the center of the image. The third image shows little evidence of activity.

Table S6

Sample ID	Indicators	Post-ex count	Frozen sect.	IHC
1	Blue/hot	926	1/1	NA
2	Hot	97	1/1	NA
3	None	No Counts	1/1	NA
4	Hot	85	0/1	NA

Intraoperative data and pathology results for excised tissue samples

Subject 7

Subject 7 is a 52 year-old female with infiltrating ductal carcinoma located at 9:00 in the right breast. The preoperative images taken with the LFOV conventional gamma camera are shown in Fig. S7-C. Preoperative images were taken with the hand-held camera are shown in Fig. S-7H.

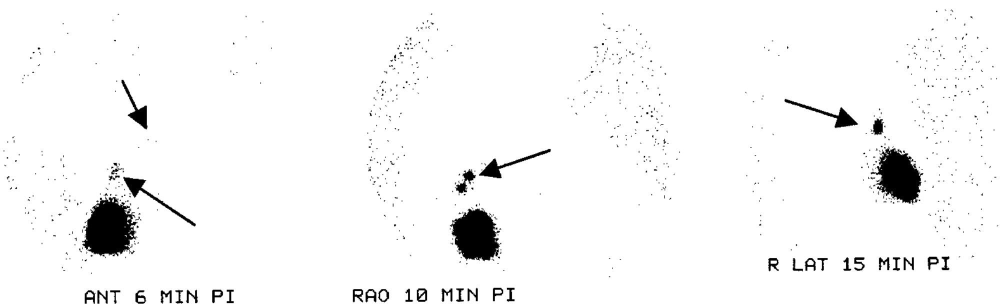
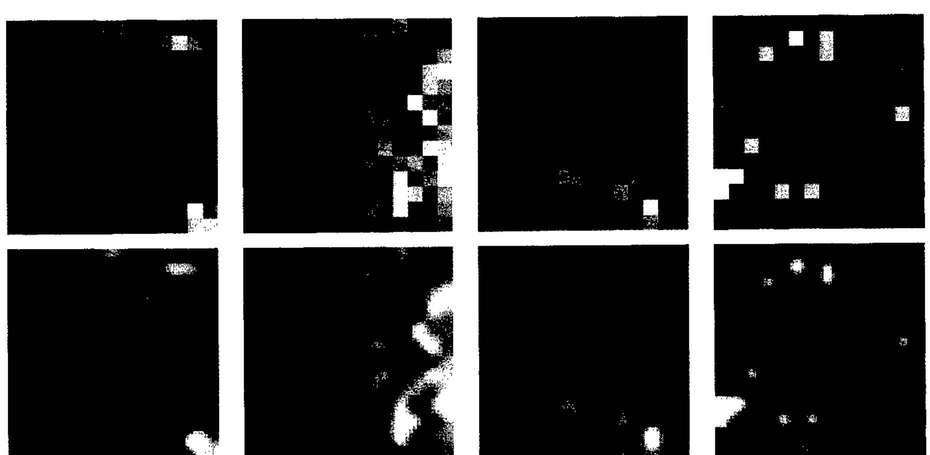


Fig. S7-C. Preoperative images taken with the LFOV conventional gamma camera. (L to R) Anterior view shows 2 foci located above the injection site. Right anterior-oblique view shows foci above of the injection site. Lateral view shows a focus located above the injection site.



Counts:	133	813	406	118
Time:	30 sec	30 sec	30 sec	30 sec

Fig. S7-H. These preoperative images were taken with the hand-held camera. The top images represent the 14-pixel x 14-pixel raw data and the bottom images are smoothed.. (L to R) The first image shows evidence of activity focus in the bottom right hand corner but the injection site is not within the FOV. The next image is shows evidence of a node but it is not fully in the FOV. The third image shows evidence of activity in the bottom right hand corner. The last image shows evidence of activity near lower left corner.

Table S7

Sample ID	**Indicators**	**Post-ex count**	**Frozen sect.**	**IHC**
1	blue/hot	4832	0/1	0/1
2	blue/hot	8510	0/2	0/2
3	blue/hot	168	0/4	0/4
4	blue/hot	72	0/1	0/1
5	blue/hot	56	0/1	0/1

Intraoperative data and pathology results for excised tissue samples.

Subject 8

Subject 8 is a 54 year-old female who has ductal carcinoma in-situ located at 12:00 in the right breast. Preoperative images taken with conventional gamma camera are shown in Fig. S8-C. The preoperative images taken with the hand-held are shown in Fig. S8-H.

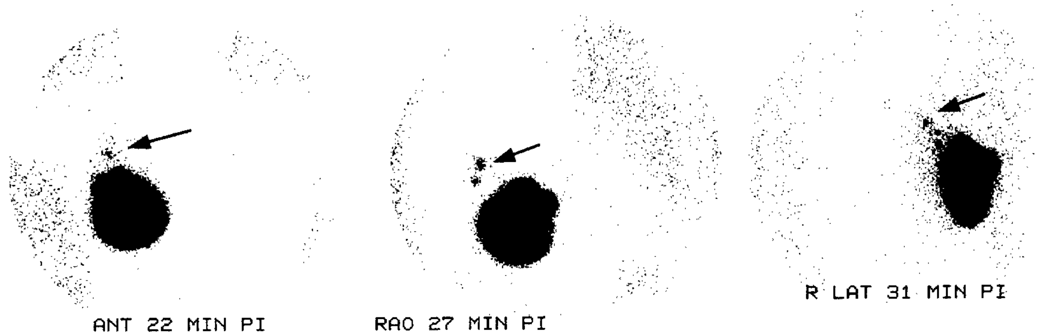
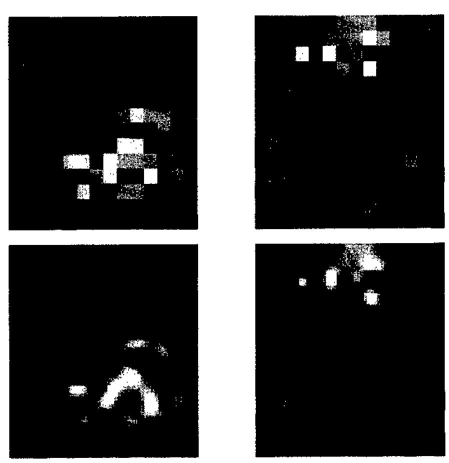


Fig. S8-C. Preoperative images taken with the LFOV gamma camera have the injection site in each image. Anterior view reveals a focus. Right anterior-oblique view reveals at least two foci. Right lateral view shows foci.



Counts:	260	168
Time:	30 sec	30 sec

Fig. S8-H. These preoperative images were taken with the hand-held camera. The top images represent the 14-pixel x 14-pixel raw data and the bottom images are smoothed. (L to R) The first image shows a node in the center of the FOV but the injection site is not in the FOV. The next image shows evidence of activity around the top.

Table S8

Sample ID	Indicators	Post-ex count	Frozen sect.	IHC
1	blue/hot	3001	0/1	0/2
2	non-blue/hot	6237	0/1	0/1
3	blue/hot	1017	0/1	0/1
4	blue/hot	1140	NA	0/1
5	blue/hot	846	NA	0/1

Intraoperative data and pathology results for excised tissue samples.

Comments
Only three of the specimens were sent for frozen section analysis. The last two specimens were not considered sentinel nodes.

Subject 9

Subject 9 is a 41 year-old female with infiltrating ductal carcinoma located at 2:00 in the left breast. The preoperative images taken with the LFOV gamma camera are shown in Fig. S9-C. The preoperative images taken with the hand-held gamma are shown in Fig S9-H.

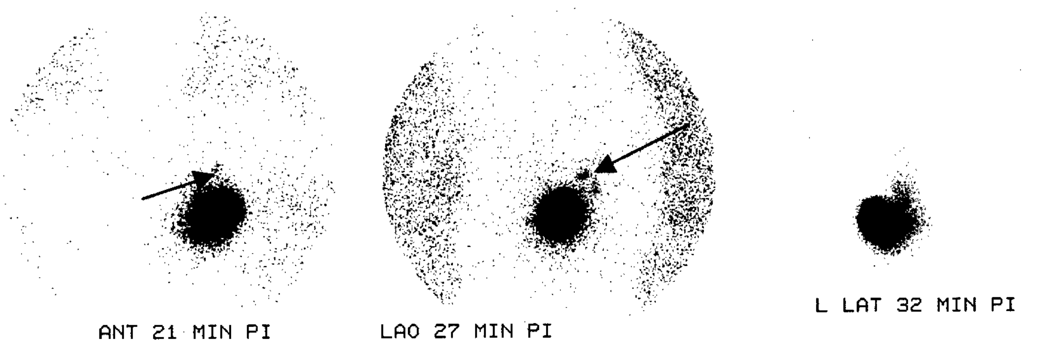
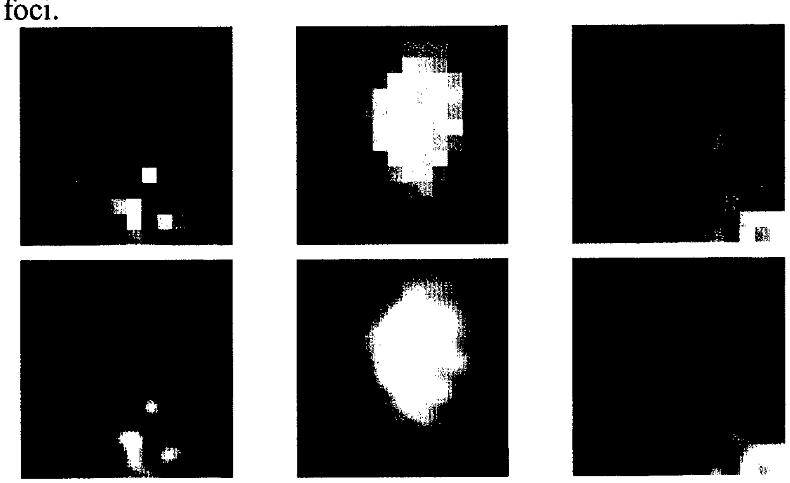


Fig. S9-C. Preoperative images taken with the LFOV gamma camera have the injection site in each image. (L to R) Anterior view of patient shows axillary focus directly above injection site. Left anterior-oblique view shows two foci above the injection site. The lateral view does not as clearly show the foci.



Counts:	393	10286	274
Time:	30 sec	30 sec	30 sec

Fig. S9-H. These preoperative images were taken with the hand-held camera. The top images represent the 14-pixel x 14-pixel raw data and the bottom images are smoothed. (L to R) The first image shows evidence of some activity but the injection site is not in the FOV of this image. The next image shows the injection site, the whole site can be imaged because the camera is held further back. The last image shows evidence of some activity in the bottom right corner of the image.

Table S9

Sample ID	Indicators	Post-ex count	Frozen sect.	IHC
1	blue/hot	1661	2/2	NA
2	non-blue/hot	567	1/1	NA

Intraoperative data and pathology results for excised tissue samples.

Comments
In the third image taken with the hand-held, Fig. S9-C, it is possible scatter from injection site covered the focus. This subject had two specimens resected and sent to frozen section, Table S9. Both samples were positive so the subject had a full axillary dissection with 0 out of 15 nodes positive.

Subject 10

Subject 10 is a 58 year-old female with infiltrating lobular carcinoma located at 12:00 in the right breast. The preoperative images taken with the LFOV are shown in Fig. S10-C. The preoperative images taken with the hand-held are shown Fig. S10-H. This subject had three specimens removed and two sent for frozen section. No nodes came back positive from frozen section.

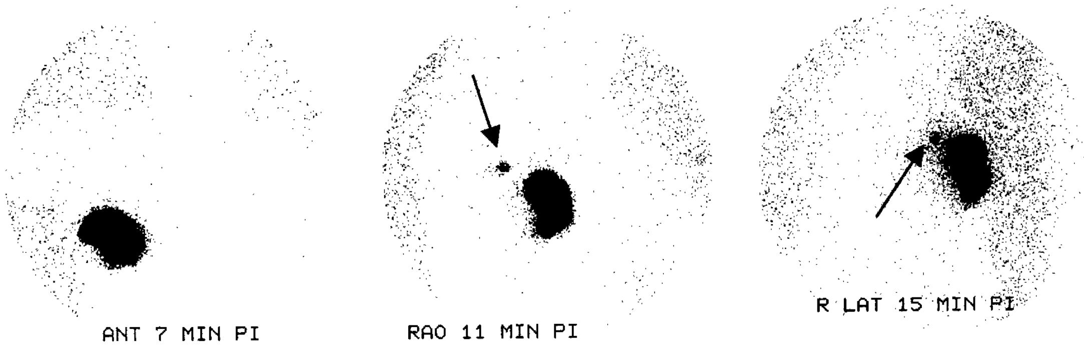
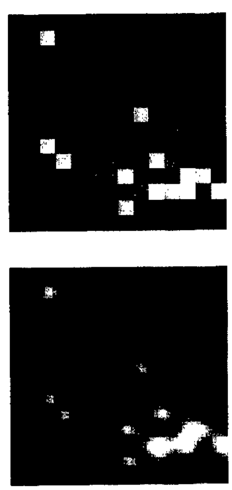


Fig. S10-C. Preoperative images taken with the LFOV gamma camera have the injection site in each image. (L to R) Anterior view of patient shows no evidence of focus. Right anterior-oblique view shows one axillary focus above the injection site. The lateral view also reveals the focus.



Counts:	109
Time:	30 sec

Fig. S10-H. This preoperative image was taken with the hand-held camera. The top image represents the 14-pixel x 14-pixel raw data and the bottom image is smoothed. The image shows evidence of some activity but the injection site is not in the FOV.

Table S10

Sample ID	Indicators	Post-ex count	Frozen sect.	IHC
1	blue/hot	5344	0/1	1/1
2	non-blue/hot	1420	0/1	0/1
3	non-blue/hot	230	NA	0/1

Intraoperative data and pathology results for excised tissue samples.

Comments
This subject had three specimens removed and two were sent for frozen section. None of the nodes came back positive from frozen section. However one node was positive on the IHC test.

Subject 11

Subject 11 is a 53 year-old female with carcinoma in located at 2:00 in the right breast. The preoperative images taken with the LFOV camera were taken the day before surgery and are shown in Fig. S11-C. .The preoperative images taken with the hand-held gamma camera are shown in Fig. S11-H.

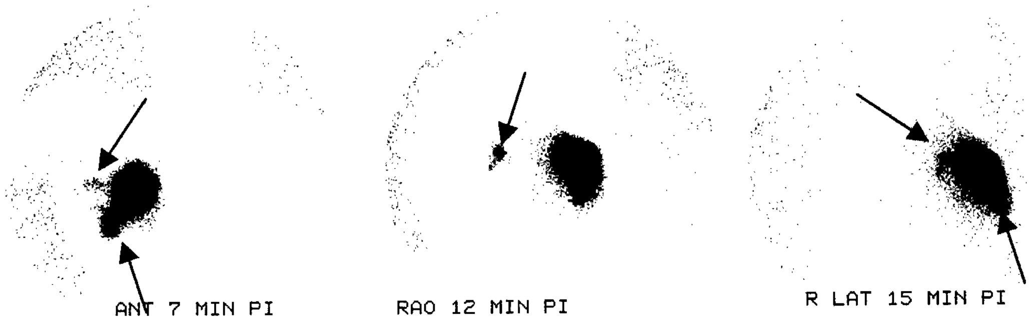
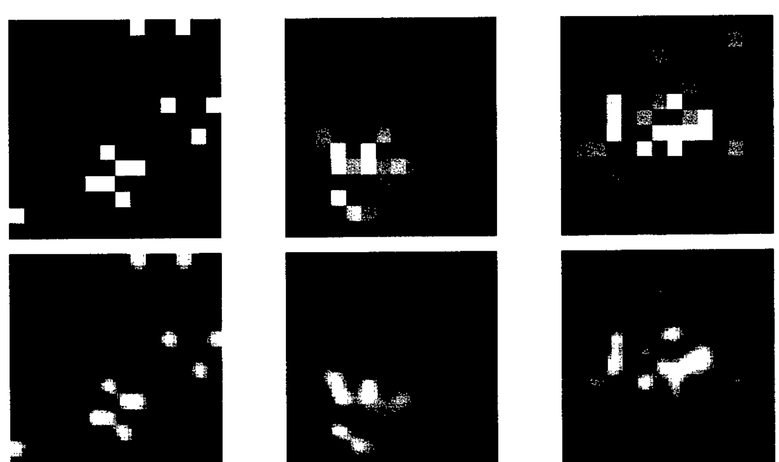


Fig. S11-C. Preoperative images taken with the LFOV gamma camera has the injection site in each image. (L to R) Anterior view reveals an axillary focus to the left and an intramammery focus below and to the left of the injection site. Right anterior-oblique view reveals the axillary focus. The lateral view reveals the axillary focus. The axillary focus cannot be distinguished.



Counts:	12	428	134
Time:	30 sec	30 sec	30 sec

Fig. S11-H These preoperative images were taken with the hand-held camera. The top images represent the 14-pixel x 14-pixel raw data and the bottom images are smoothed. (L to R) The first image has very few counts and was most likely not taken over a hot node. The next image shows evidence of activity from a node. The last image shows evidence of activity from a node.

Table S11

Sample ID	Indicators	Post-ex count	Frozen sect.	IHC
1	blue/hot	3214	0/1	0/1
2	blue/hot	1927	0/1	0/1

Intraoperative data and pathology results for excised tissue samples.

Subject 12

Subject 12 is a 67 year-old female with infiltrating ductal carcinoma located at 9:00 in her left breast. The preoperative images taken with the LFOV conventional gamma camera are shown in Fig. S12-C. The preoperative images taken with the hand-held camera are shown Fig. S12-H.

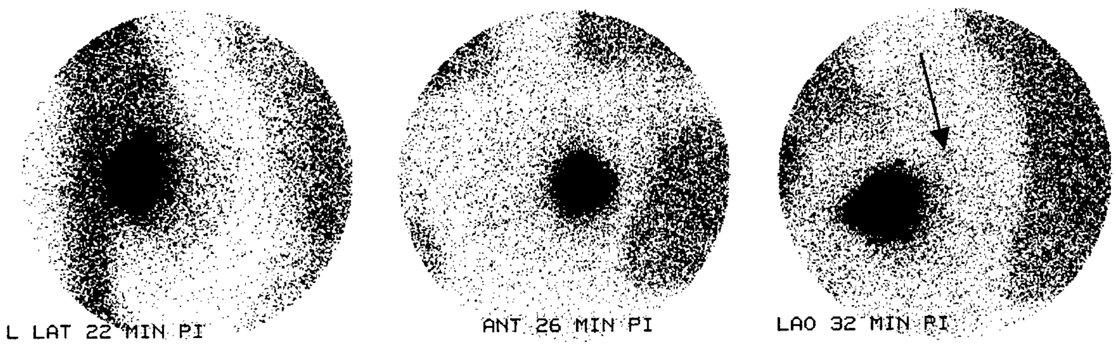
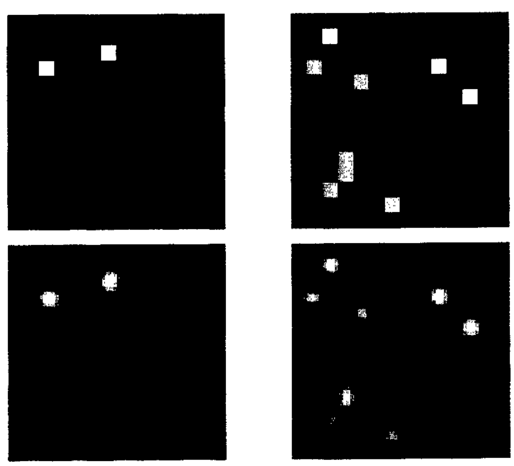


Fig. S12-C. Preoperative images taken with the LFOV gamma camera has the injection site in each image. (L to R) The left lateral view does not clearly reveal focus. Anterior view does not clearly show a focus.. Left anterior-oblique view shows an axillary focus clearly.



Counts:	43	98
Time:	30 sec	30 sec

Fig. S12-H. These preoperative images were taken with the hand-held camera. (L to R) The first image does not show evidence of a node. The second image shows some evidence of more activity, but no distinct focus.

Table S12

Sample ID	Indicators	Post-ex count	Frozen sect.	IHC
1	blue/hot	588	0/?	0/2
2	blue/hot	543	0/1	0/1

Intraoperative data and pathology results for excised tissue samples.

Comment
This was a difficult case to do preoperative imaging.

Subject 13

Subject 13 is a 42 year-old female with ductal carcinoma in-situ located at 10:00 in the right breast. The preoperative images taken with LFOV gamma camera are shown in Fig. S13-C. The preoperative images taken with the hand held camera are shown in Fig. S13-H.

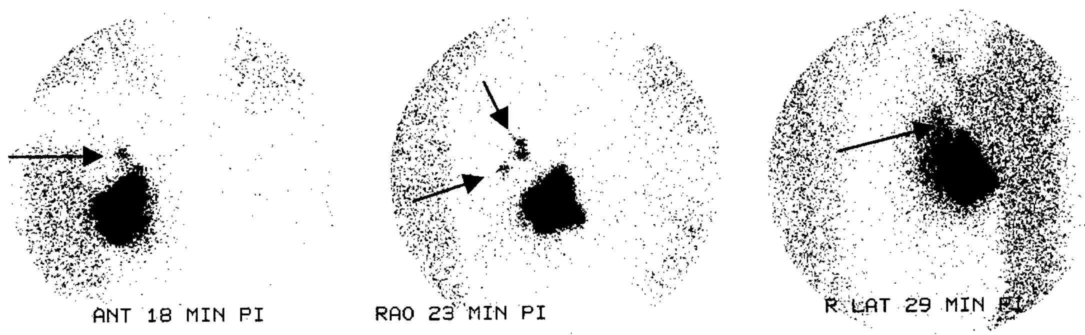
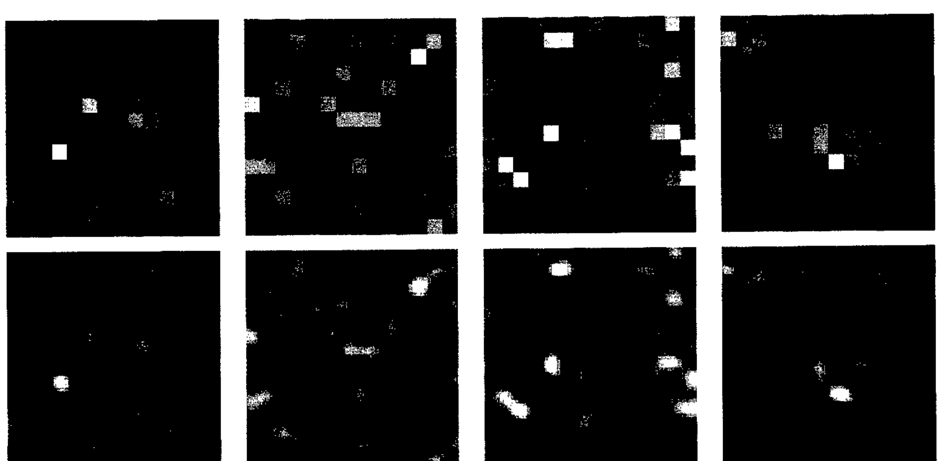


Fig. S13-C. Preoperative images taken with the LFOV gamma camera has the injection site in each image. (L to R) Anterior view reveals an axillary focus above the injection site. Right anterior-oblique view shows multiple axillary foci. In the lateral view does not clearly show a focus.



Counts:	212	426	476	334
Time:	15 sec	30 sec	30 sec	30 sec

Fig. S13-H. These preoperative images were taken with the hand-held camera. The top images represent the 14-pixel x 14-pixel raw data and the bottom images are smoothed. (L to R) All images have some evidence of activity but no reference to location.

Table S-13

Sample ID	Indicators	Post-ex count	Frozen sect.	IHC
1	blue/hot	5788	0/1	0/1
2	blue/hot	5322	0/?	0/2
3	blue/hot	1832	0/1	0/1
4	non-blue/hot	3737	0/1	0/1
5	non-blue/hot	1413	0/1	0/1

Intraoperative data and pathology results for excised tissue samples.

Subject 14

Subject 14 is a 56 year-old female with infiltrating ductal carcinoma located at 12:00 in the left breast. Preoperative images done with LFOV gamma camera are shown in Fig. S14-C. The preoperative images taken by the hand-held are shown in Fig. S14-H.

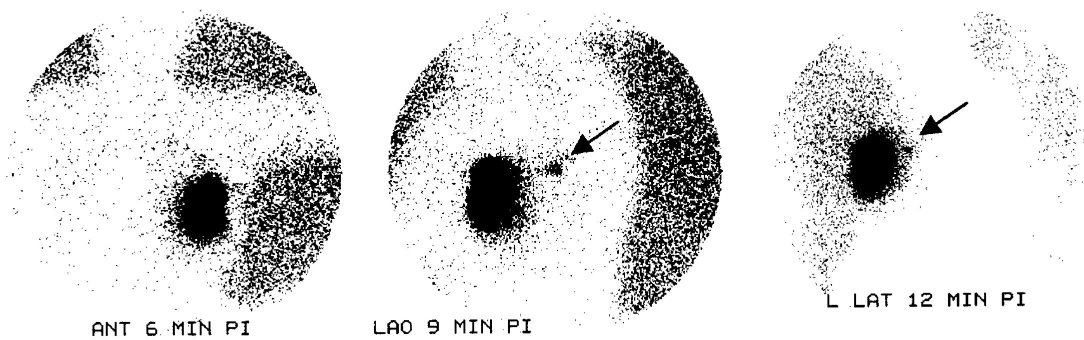
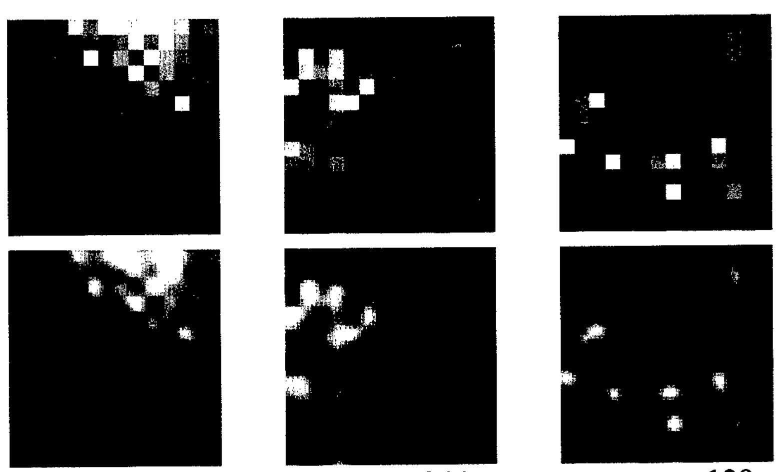


Fig. S14-C. Preoperative images taken with the LFOV gamma camera have the injection site in each image. (L to R) Anterior view does not clearly reveal a focus. Left anterior-oblique view shows an axillary focus. In the lateral view a focus is also visualized.



Counts:	450	244	129
Time:	30 sec	30 sec	30 sec

Fig. S14-H. These preoperative images were taken with the hand-held camera. The top images represent the 14-pixel x 14-pixel raw data and the bottom images are smoothed. (L to R) The first two images show evidence of focal activity. The last image does not.

Table S-14

Sample ID	Indicators	Post-ex count	Frozen sect.	IHC
1	blue/hot	5774	0/?	1/3
2	blue/hot	856	0/?	0/4

Intraoperative data and pathology results for excised tissue sample.

Appendix III

Paper presented at IEEE 2002 Meeting:

Gamma Cameras for Intraoperative Localization of Sentinel Nodes: Technical Requirements Identified Through Operating Room Experience

Gamma Cameras for Intraoperative Localization of Sentinel Nodes: Technical Requirements Identified Through Operating Room Experience

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Abstract*-- Various nuclear medicine techniques are used for localization of sentinel lymph nodes (SLNs). Procedures that include high-quality preoperative imaging and skilled intraoperative use of a gamma counting probe are almost always successful. Those that involve only the intraoperative use of a gamma probe are generally less successful. For a variety of reasons, high-quality preoperative imaging is not possible at many institutions and thus many institutions use procedures that involve only intraoperative use of a gamma probe. It has been proposed that procedures involving intraoperative imaging be developed and evaluated. To better identify technical requirements for an intraoperative imaging system and protocol, five breast cancer patients were imaged intraoperatively, as well as preoperatively. The intraoperative imaging was performed using a small (127 mm × 127 mm) field-of-view (FOV) gamma camera mounted on an articulating arm (Gamma Medica GammaCAM/OR). Intraoperative imaging was performed following administration of anesthesia and following preparation of a sterile surgical field about the involved breast. The camera and arm were draped in a sterile sheath, and the operators of the camera were attired in sterile surgical wear. Intraoperative images were acquired pre-incision and post-excision. Images were acquired for 2 to 3 minutes each. Members of the surgical/nuclear medicine team observed and assessed the ease or difficulty of the acquisitions of images. Conclusions included that a camera for SLN localization should exhibit low noise, should have very good shielding from all non-imaging directions, should have very low collimator penetration, and should have very good sensitivity at 140 keV. The system should have tools for flexible display windowing, convenient region-of-interest definition, and rapid image analysis. These features should be readily available and be easily controlled by the individual positioning the camera. The FOV should be at least 127 mm × 127 mm but probably no larger than 200 mm × 200 mm. A system should also have a means by which its camera can be easily repeatably positioned.

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I. Introduction

STAGING of breast cancer requires assessment of lymph nodes – are any nodes metastatic? A decade ago, the most common approaches involved full resection of axillary nodes. Such approaches produce accurate stagings of breast cancers; they also often produce significant morbidity. Today, approaches that involve only excision of sentinel nodes – approaches that are tissue sparing and less morbid – often replace those requiring full axillary resection.

The goal of a sentinel lymph node (SLN) procedure is the accurate determination of the absence or presence of cancer in the SLNs of a tumor – the nodes to which lymphatic fluid first drains as it clears from a tumor or the tissue surrounding a tumor. The premise is if all SLNs are free of metastases, then all other nodes are as well. A SLN procedure should detect all SLNs of a tumor and should produce an accurate assessment of each detected SLN. Ideally, assessment of SLNs would be in vivo. Such assessment is presently not possible, and detected SLNs are excised and histologically evaluated.

Nuclear medicine techniques are used in many SLN protocols, including many for breast cancer patients. All such protocols involve injection of a technetium-99m (Tc-99m) labeled colloid and preoperative imaging and/or intraoperative counting of gamma emissions from accumulations of colloid.

When high-quality preoperative imaging with a conventional gamma camera and skilled intraoperative counting with a gamma probe are performed, efforts to detect and localize SLNs are almost always successful. When protocols that include only intraoperative counting are used, efforts are often less successful.

The context of this work is development and assessment of SLN protocols that include intraoperative imaging of SLNs with small FOV gamma cameras. The limited reports on intraoperative SLN imaging are Ref. [1]-[3]. One speculation is use of protocols with intraoperative imaging and counting, or with preoperative imaging and intraoperative imaging and counting, can increase the success rates of practitioners at sites where preoperative imaging is not sufficiently successful.

Reported here are results of an initial investigation in which a prototype small FOV gamma camera was used for intraoperative imaging of SLNs in breast cancer patients.

II. Methods

Five breast cancer patients scheduled for surgery including a sentinel lymph node (SLN) procedure were enrolled in this study approved by the Internal Review Board overseeing research at Emory University and the Atlanta Veterans Affairs Medical Center. Management of the patients as subjects included all the procedures they would have received if they had not enrolled in the study. Some of these are injections of radiolabeled colloid, preoperative imaging, injections of blue dye, intraoperative gamma counting, and pathology analysis of excised tissues. In addition, management of the subjects included procedures to image intraoperatively the patients and some of the tissues excised during surgery. This imaging was performed using a novel nuclear medicine system with a small field-of-view (FOV) gamma camera [4], [5].

A. Subjects

Five female breast cancer patients were enrolled in this study. Table 1 summarizes some subject characteristics, including age, breast size, disease location, and disease type.

Table I.
Subject Summary

Subject	Age	Size	Disease Location	Disease Type
1	59	A	Right @ 3:00	lobular carcinoma in situ
2	58	C	Left @ 2:00	infiltrating lobular carcinoma
3	40	D	Right @ 9:00	infiltrating ductal carcinoma
4	64	D	Left @ 2:00	infiltrating ductal carcinoma
5	58	C	Right @ 10:00	infiltrating lobular ductal carcinoma

B. Radiopharmaceutical Injections

Each subject, on the day of surgery, was prepared for preoperative imaging and positioned on an imaging table. There the subject received three injections of 0.22-μm filtered Tc-99m sulfur colloid. Two injections were peritumoral; each of these was 125 μCi in 1.0 ml. The third was subdermal; it was 250 μCi in 0.3 ml. All three syringes were shaken before the injections to help insure that the colloid was suspended in solution and well mixed. Following the third injection, the breast was massaged for 1 to 5 minutes to enhance migration of the tracer into the lymphatic system.

C. Preoperative Imaging

Preoperative imaging was performed using a conventional single-head gamma camera (General Electric 500). This imaging commenced immediately after the radiotracer injections and massage. Images acquired included anterior, lateral, and oblique views. A cobalt-57 flood source was used to produce on each preoperative image an outline of the subject's body contour. As necessary, each subject's involved breast was positioned or held so as to insure that emissions from focal uptakes had minimal attenuation paths.

The first images acquired of each subject were a series that recorded dynamics of tracer migration. Such images often record the order in which multiple nodes are visualized, providing information relevant to identification of nodes as sentinel or secondary.

Once SLN foci were located, anterior and lateral marks were inked on the skin to provide the surgeon a starting point for intraoperative node localization using a counting probe.

D. Blue Dye Injections

After the start of administration of anesthesia, the surgeon injected isosulfan blue dye (3 to 5 injections with a total volume of 5 cc) and massaged the breast for 1 to 5 minutes.

E. Intraoperative Imaging

Several intraoperative images of each subject were acquired using a mobile system with a small field-of-view (FOV) gamma camera and an articulating positioning arm (Gamma Medica GammaCAM/OR) (Fig. 1). The 127 cm × 127 cm (5 in × 5 in) FOV camera comprises a low-energy high-resolution (LEHR) collimator, 56×56 array of 2 mm × 2 mm × 6 mm NaI(Tl) crystals, and a 5×5 array of 1 in × 1 in position-sensitive photomultiplier tubes (PSPMTs). The camera and arm were draped in a sterile sheath, and the operators of the camera were attired in sterile surgical wear.

Pre-incision images of regions that exhibited focal uptake on the preoperative images were acquired for 120 to 180 seconds. Post-excision images of the same regions were acquired for up to 300 seconds to assess the success of excision and to look for residual activity. Image-display windowing was varied during acquisitions to verify the presence or absence of weak accumulations of tracer.

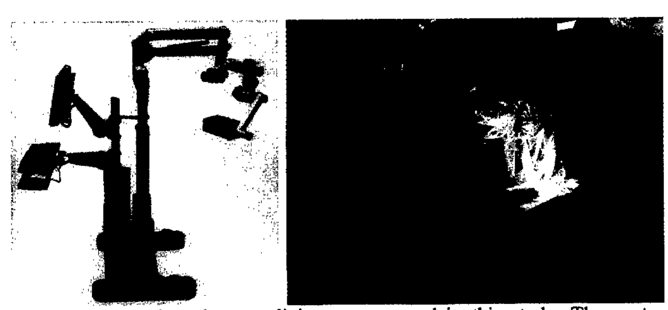

Fig. 1. The novel nuclear medicine system used in this study. The system (Gamma Medica GammaCAM/OR) includes a small FOV gamma camera, a positioning arm, a mobile support stand, and a computer system (left). In the surgical suite, when used for imaging within the sterile field, the camera and positioning arm are draped in a sterile sheath (right).

F. Intraoperative Counting

When acquisition of pre-incision images was complete, the surgical procedure proceeded per standard protocol. This included the use of a gamma counting probe (Carewise C-Trak) covered by a sterile sheath. For each detected focus, the surgeon obtained 10-sec acquisitions of background counts, pre-incision counts, and post-excision counts.

G. Specimen Imaging

All excised tissues were imaged for 120 to 180 seconds using the small FOV camera as shown in Fig. 2. The activity in each specimen was determined using the camera's sensitivity of 135 cpm/μCi.

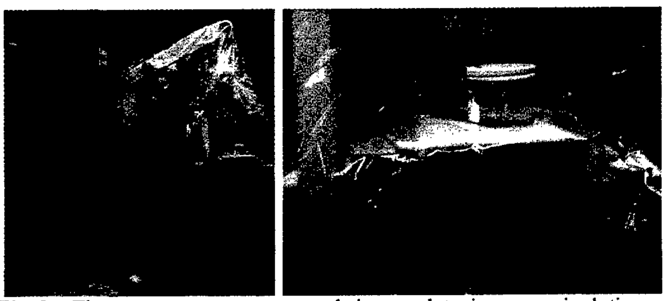

Fig. 2. The gamma camera system being used to image excised tissues. Specimen imaging was performed intraoperatively under sterile conditions.

III. Example Cases

In this section, we provide data from the procedures of two of the five subjects enrolled in this study. Data from the procedures of the other three are similar.

A. Case 1

Subject is a female age 59 with lobular cancer in situ located at 3:00 in the right breast.

Preoperative images are shown in Fig. 3; intraoperative pre-incision, post-excision, and post-lumpectomy images in Figs. 4 and 5; and intraoperative specimen images in Fig. 6.

Five specimens were excised from the right axilla of this subject. Table II summarizes properties of the specimens. Analysis of the specimen images indicates each contained between 0.1 and 1.5% of the injected dose – between 250 and 3750 nCi at the time of imaging, about 4 hours post injection (pi). All five specimens were negative for metastasis; specimens 1, 3, and 4 were blue; 2 and 5 were not blue.

Table II

Summary of Specimens for Case 1

Specimen	Counts (probe)	Activity (nCi) (camera)	Specimen/ Injected Activity (%)
1	7958	3740	1.46
2	1262	376	0.15
3	3190	459	0.18
4	829	267	0.11
5	2085	300	0.12

We note that counts from a hand-held probe may not accurately reflect relative activities in specimens. Probe count rates are very sensitive to probe positioning and to the distribution of activity within a specimen. This can be seen in Table II by comparing the ratios of probe counts to the corresponding ratios of camera-determined activities.

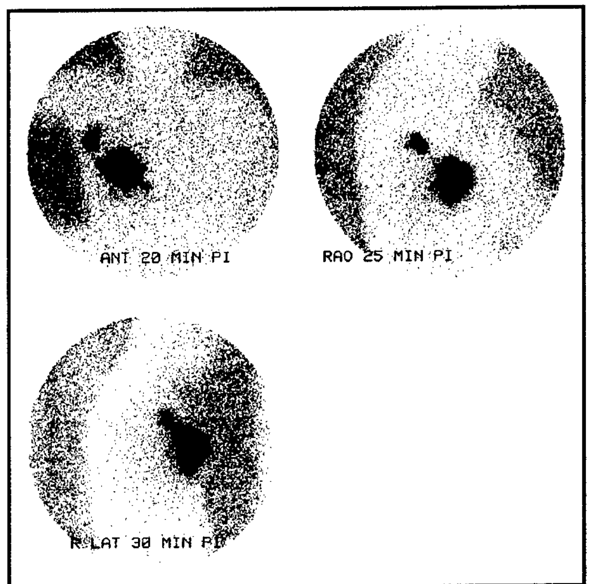

Fig. 3. Three preoperative images acquired for subject one. The images are anterior taken 20 min pi (upper left); right anterior oblique taken 25 min pi (upper right), and right lateral taken 30 min pi (lower left). Each image represents a 5-min acquisition. The large focus is activity in the injection site. There are several axillary foci. Three are visible at the window settings of the images; five radioactive specimens were removed during surgery. An internal mammary focus is visible on the anterior image.

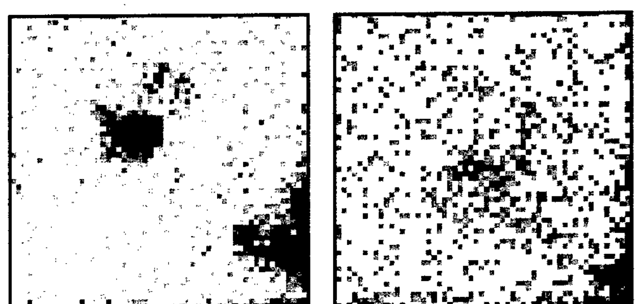

Fig. 4. Right anterior oblique 30-degree pre-incision image and 45-degree post-excision image acquired with the small FOV gamma camera. The left image is a 2-min image that indicates the presence of at least three foci of radioactivity. The right image is a 3-min image acquired after the excision of five radioactive tissue specimens.

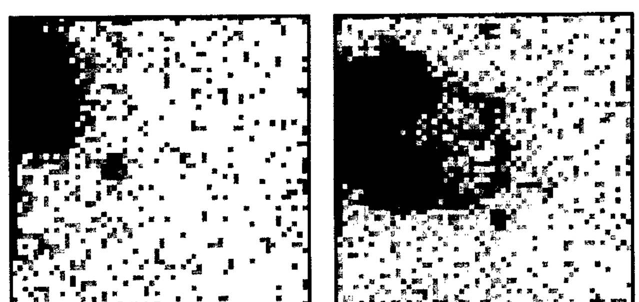

Fig. 5. Anterior pre- and post-lumpectomy images acquired with the small FOV gamma camera. The left image is a 2-min image acquired pre-lumpectomy. The right image is a 2.5-min image acquired post-lumpectomy. The images show two internal mammary foci. The surgeon chose not to remove any internal mammary nodes. Note that the lumpectomy procedure altered the distribution of tracer in the injection site.

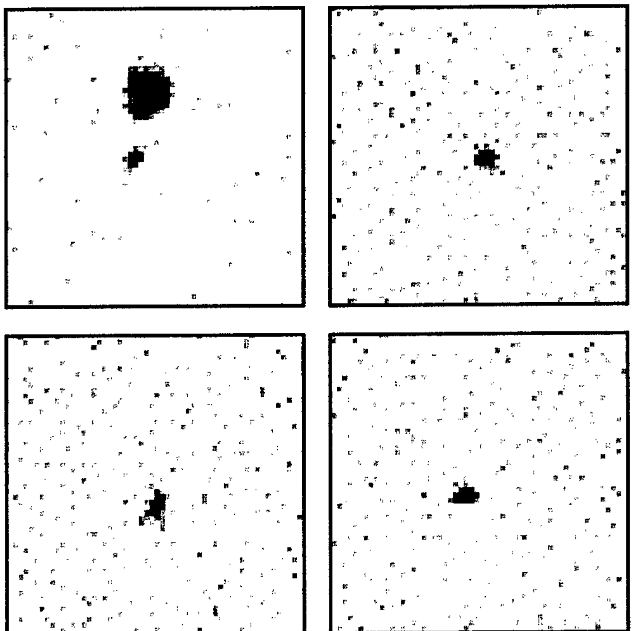

Fig. 6. Intraoperative images of the five tissue specimens excised from subject one. The first two specimens were imaged simultaneously (upper left). The other three specimens were imaged separately (upper right, lower left, and lower right). Each image was acquired for 3 minutes.

B. Case 2

Subject is a female age 40 with infiltrating ductal carcinoma located at 9:00 in the right breast.

Preoperative images are shown in Fig. 7; pre-incision intraoperative images in Fig. 8; post-excision intraoperative iamges in Fig. 9; and an intraoperative specimen image in Fig. 10.

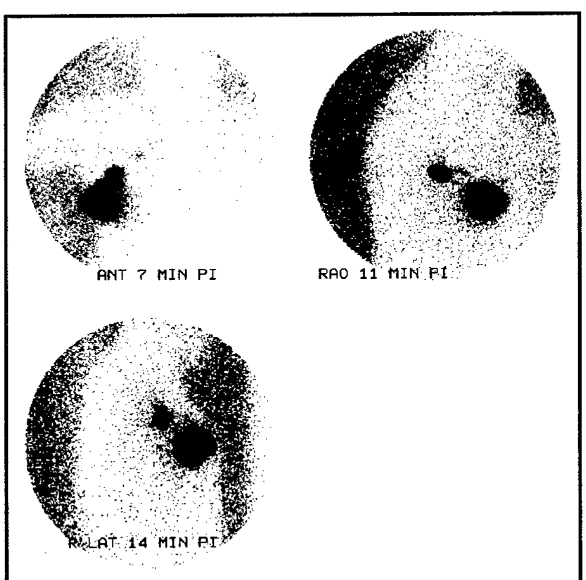

Fig. 7. Three preoperative images acquired for subject two. The images are anterior taken 7 min pi (upper left); right anterior oblique taken 11 min pi (upper right); and right lateral taken 14 min pi (lower left). Each image represents a 3-min acquisition. The large focus is activity in the injection site. There are several axillary foci; two are visible at the window setting of the images. One radioactive specimen (with two nodes at pathology) was removed in surgery. Three lymphatic channels are visible on the right lateral image.

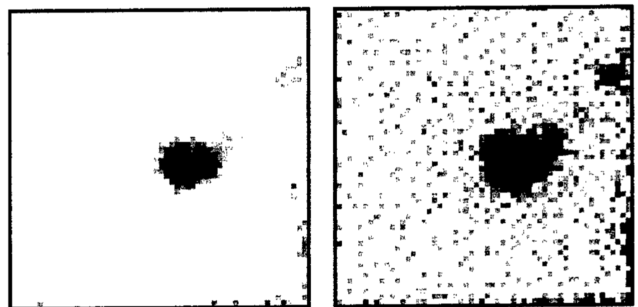

Fig. 8. Right anterior oblique 45-degree pre-incision image acquired with the small FOV gamma camera. The data displayed in the two images are the same. The data represent a 3-min acquisition. The left image indicates the presence of at least three foci. The right image emphasizes a less visually intense focus. The surgeon chose not to remove the anatomically secondary node corresponding to this less visually intense focus.

One 7.0 cm × 6.0 cm × 1.0 cm tissue specimen was excised from the right axilla of this subject; radioactivity was detected and blue dye was visible. Intraoperative imaging indicated activity of about 4.5% of the injected dose (approximately 13,000 nCi at the time of imaging, about 4 hours pi). Note that this magnitude of activity in a specimen is unusual, as uptake in an SLN is typically 1.0% or less.

The specimen contained two nodes: one 2 cm in diameter, the other 4 cm. Both nodes were negative for metastases.

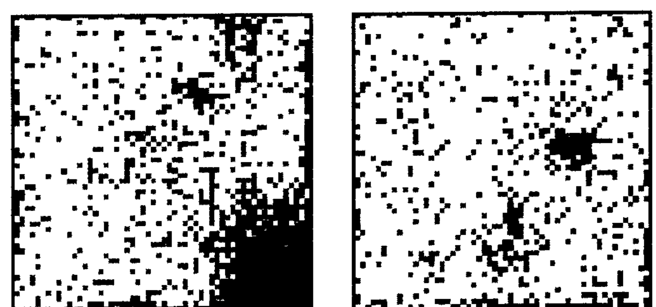

Fig. 9. Anterior post-excision images acquired with the small FOV gamma camera. Each image represents a 2-min acquisition. The left image shows minimal residual activity at the excision site corresponding to the two most intense foci in the left image of Fig. 8. The right image shows that the less intense focus of Fig. 8 remains "post-excision". This is the case because the surgeon chose not to remove tissue at that site of tracer accumulation.

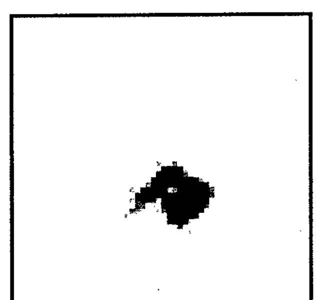

Fig. 10. Intraoperative image of the tissue specimen excised from subject two. The image suggests the specimen comprises more than one node. Two nodes were identified in pathology.

IV. Observations

The objective of this short-series study was initial evaluation of a nuclear medicine system with a small FOV gamma camera for the tasks of intraoperative detection and localization of SLNs in breast cancer patients.

Observation 1. A small FOV camera for intraoperative imaging for detection and localization of SLNs should have very uniform response over its full FOV, very good sensitivity to 140 keV gamma emissions, very low collimator penetration, and very good radiation shielding from all non-imaging directions.

The camera should be such that any focus of counts on an image represents a true accumulation of radiotracer in a patient. The goals of imaging in a SLN procedure are detection and localization of tracer accumulations that might represent SLNs. It is desirable that such accumulations be detected and located quickly, particularly if these tasks are being performed after administration of anesthesia, that is, being performed intraoperatively.

Observation 2. A system for intraoperative imaging of SLNs should have excellent, easily controlled tools for gray-scale windowing of images, for rapid definition of ROIs, and for rapid statistical analysis and characterization of ROIs.

These tools should be such that an individual positioning the camera during surgery can manipulate them easily. Note that the individual in this context is wearing sterile surgical garb and using the camera in a sterile surgical field.

Observation 3. A system for intraoperative imaging of SLNs need not have "high" resolution. It should have high sensitivity.

Very good sensitivity is more important than very good resolution for the tasks of detection and localization of SLNs. The authors from the Atlanta VAMC and Emory University have successfully imaged preoperatively foci of radiotracer accumulation in 214/214 patients managed by the authors. This has been done using relatively small doses of radiotracer, approximately 0.5 mCi/patient, and a GE 500 camera with a low-energy all-purpose (LEAP) collimator – sensitivity approximately 300 cpm/μCi and resolution approximately 10 mm at the normal imaging distance of 10 cm.

Observation 4. A system for intraoperative imaging of SLNs should have a camera that can be easily positioned and easily repositioned.

Easily positioned means that a camera's support system has ranges of motion in three dimensions that fully cover the area/volume to be imaged and means that all desired motions can be performed in an essentially effortless manner by the operator. Easily repositioned means the camera can be positioned, be moved out of the surgical field during foci excision, and be repositioned post excision such that it is in the pre-excision location and orientation. Ideally, a system has a means of correlating an image being acquired with the physical location of the area/volume being imaged.

Observation 5. A system for intraoperative imaging of SLNs should have a camera with a FOV and housing small enough that the camera can be placed in close proximity to each area/volume to be imaged and large enough that all areas to be surveyed can be imaged in an acceptable time.

The region to be surveyed in a search for SLNs in breast cancer patients is approximately 250 mm × 500 mm. If only intraoperative imaging is performed on a patient, an area that size will likely need to be surveyed. To do this, one must acquire at least 8 images when using a camera with a 127 mm × 127 mm FOV. To insure that even reasonably low-count foci are detected, each image should be acquired for at least 3 minutes. This implies a full survey conducted with a camera with a 127 mm × 127 mm FOV takes a minimum of 20 minutes and more likely 30+ minutes if the times for positioning and for acquisition of additional views are included. A camera with a 150 mm × 200 mm FOV or 200 mm × 200 mm FOV would likely reduce the number of images needed; but such cameras would also require more substantial positioning arms as they will have significantly more weight if they are designed and constructed using similar technologies.

V. Discussion

Time is a critical commodity in a surgical suite. Thus, any intraoperative imaging added to the management protocol of a breast cancer patient should reduce surgical time or provide sufficient added clinical value to justify any addition of time to the surgical procedure. We believe a system for intraoperative use in breast cancer SLN procedures should have the following properties. First, the system's camera should be very sensitive so that accumulations of tracer can be detected quickly. Second, the camera's FOV should be such that imaging of all regions of relevant nodes can be completed quickly. Third, the system should have a sophisticated positioning arm that makes it easy to position the camera for close-proximity imaging, to position the camera for acquisition of tiled images of all regions of relevant nodes, and to reposition the camera quickly and accurately for excision site assessment and residual mapping. Fourth, the system should have excellent display windowing properties and controls so nodes with limited uptake can be quickly detected and located even if located near the injection site.

VI. References

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