CASE COMPREHENSIVE CANCER CENTER

STUDY NUMBER:	CASE 10114
STUDY TITLE:	COMPARISON OF USE OF INDOCYANINE GREEN AND 99mTc-LABELED RADIOTRACER FOR AXILLARY LYMPHATIC MAPPING IN PATIENTS WITH BREAST CANCER
PRINCIPAL INVESTIGATOR:	Stephen R. Grobmyer, MD Department of General Surgery Cleveland Clinic 9500 Euclid Avenue Cleveland, OH 44195 (216) 636-2843, grobmys@ccf.org
CO-PI:	Alicia Fanning, MD Department of General Surgery Cleveland Clinic 9500 Euclid Avenue Cleveland, OH 44195 (216) 444-3334, fannina@ccf.org
CO- INVESTIGATORS:	Robyn Stewart, MD Department of General Surgery Cleveland Clinic 9500 Euclid Avenue Cleveland, OH 44195 (216) 444-6293, stewarr5@ccf.org Stephanie Valente, DO Department of General Surgery Cleveland Clinic 9500 Euclid Avenue Cleveland, OH 44195 (216) 444-0769, valents3@ccf.org Diane Radford, MD Department of General Surgery Cleveland Clinic 9500 Euclid Avenue Cleveland, OH 44195 (216) 444-7506, radford2@ccf.org
STATISTICIAN:	Chao Tau Quantitative Health Sciences Cleveland Clinic 9500 Euclid Avenue Cleveland, OH 44195 (216) 445-8350, tuc@ccf.org

SUPPORT: CCF Breast Services Division

CLINICAL FACILITY: Cleveland Clinic

APPROVALS: Protocol Review and Monitoring Committee: Approved
Cleveland Clinic IRB: Approved

STUDY COORDINATORS:

Courtney Yanda
Cleveland Clinic
9500 Euclid Avenue
Cleveland, OH 44195
(216) 444-3159, yandac@ccf.org

Barbara BeVier
Cleveland Clinic
9500 Euclid Avenue
Cleveland, OH 44195
(216) 445-9159, bevierb@ccf.org

TABLE OF CONTENTS

1.0 INTRODUCTION

Background:

Lymphatic mapping and axillary sentinel node biopsy has become a standard procedure for the surgical staging of patients with early stage breast cancer. It has been shown to be safe and accurate and limits significantly the need for traditional axillary dissection in many patients with early stage breast cancer. Traditionally, lymphatic mapping has involved the use of ^{99m}Tc-labeled radiotracer, or visible blue dye (methylene blue or isosulfan blue dye), or a combination of ^{99m}Tc-labeled radiotracer and visible blue dye. Sentinel nodes are defined as axillary lymph nodes in which there is the accumulation of one or more of these tracers or dyes.

The use of ^{99m}Tc-labeled radiotracer has a long history and is one of the more commonly used techniques of identifying sentinel nodes. However, the use of radiotracers has significant limitations including the requirement for nuclear licensing; the need to prepare, handle and dispose of nuclear material, patient inconvenience with painful injections typically occurring before surgery.

There is a growing body of literature supporting the role of indocyanine green (ICG) dye for lymphatic mapping in Europe and Japan. ICG is a fluorescent dye which can be detected using near infrared cameras. The use of ICG in conjunction with a near infrared camera offers many potential advantages over the use of other techniques including the ability to inject the material while the patient is under anesthesia in the operating room, the ability to use near infrared imaging to directly visualize lymphatic flow, and no special material handling is required. ICG is FDA approved for vascular fluorescence and liver function studies in humans.

ICG is a di-sulfonated heptamethine indocyanine with moderate optical properties, which emits ≈ 800 nm. There are many uses for ICG during image-guided surgery. After intravenous injection, it can be used for NIR angiography of blood vessels, identification of the extrahepatic bile ducts, and identification of liver metastases. After subcutaneous injection, ICG has been reported by numerous authors to be safely used for sentinel lymph node (SLN) mapping(1-5) and assessing lymphatic function."(6)

ICG has been used for the last 50+ years as a visible dye (green for ICG). Thus, there is an unprecedented body of clinical data regarding their safety when used at millimolar concentrations." (6) The use of ICG for lymphatic mapping in breast cancer patients has been demonstrated to be safe in numerous human studies performed in Asia and Europe (7-11). There is a recent retrospective case series report of using ICG for lymph node mapping in patients with melanoma from the Cleveland Clinic documenting its safety for in human use and lymphatic mapping (12).

A recent study from Europe has demonstrated high concordance between the number nodes identified with ICG and ^{99m}Tc-labeled radiotracer (11). There has been very limited work on the use of ICG for axillary lymph node mapping in humans in the United States, and no comparison studies of ICG with ^{99m}Tc-labeled radiotracer. The goal of the project is to confirm that axillary lymphatic mapping with ICG leads to a similar number of nodes being labeled as sentinel as lymphatic mapping with ^{99m}Tc-labeled radiotracer. Successful completion of this project would support the use of ^{99m}Tc-labeled radiotracer with ICG for LN mapping in early stage breast cancer patients.

2.0 OBJECTIVE

Hypothesis:

ICG is equivalent to 99mTc-labeled radiotracer for axillary lymphatic mapping in patients with early stage breast cancer in terms of the numbers of nodes identified as sentinel by each method being similar.

3.0 STUDY DESIGN

Methods:

Patients with a confirmed diagnosis of clinical stage 1 or 2 breast cancer who are undergoing breast cancer surgery with lumpectomy or mastectomy and planned axillary sentinel node biopsy procedure will be eligible for the study. Patients with cancer > 3cm, clinically positive nodes, prior surgery for breast cancer in the index breast, bilateral sentinel lymph node mapping, thyroid dysfunction, hypersensitivity to iodine, and hepatic or renal insufficiency will be excluded from the study.

- We plan to enroll approximately 130 adult female patients who will be identified in the breast clinic at Cleveland Clinic Main Campus.
- Informed consent will be obtained.
- Patient information will be collected from the medical record and entered in Redcap.

Patients will undergo lymphatic mapping with ^{99m}Tc sulfur colloid in accordance with routine clinical practice. Injections of ^{99m}Tc sulfur colloid will take place the afternoon prior to planned next morning surgery or on the morning of surgery. Patients will undergo lymphoscintigraphy in accordance with standard clinical practice.

Immediately prior to operation, after the induction of anesthesia in the operating room, up to 1cc of 0.5% ICG solution will be injected subdermally or intradermally close to, above the tumor,into the subareolar region or into the periareolar region after disinfection of the breast skin. ICG movement will be facilitated by manual massage and monitored with fluorescence imaging. ICG fluorescence will be elicited and detected by PDE camera (Hamamatsu Photonics, Hamamatsu, Japan) which has FDA 510(k) clearance to visualize ICG fluorescence in the humans for vascular imaging. The lymphatic drainage, made evident by the fluorescent dye, will be monitored in real time on a monitor. The fluorescence will be followed towards the axilla and time for the fluorescence to reach the axilla will be recorded. In accordance with standard practice, an incision will be made in the axilla. Fluorescent lymph nodes (ICG positive) will be localized and removed and sent for pathologic analysis as per standard surgical practice. Node removal will continue until no residual fluorescence is visible in the axilla. Excised nodes will be tested for radioactivity using a standard gamma-detecting probe and the counts per minute will be recorded. Finally, the axillary region will be inspected with the gamma probe to determine if there are any residual radioactive nodes. Residual sentinel nodes will be removed. With regard to radioactivity, sentinel nodes are defined as any node with at least 10% of the hottest nodal counts.

The following information will be collected for each removed node:

1. Fluorescence (yes/no)
2. Counts per minute
3. Pathologic status of node (no metastasis, isolated tumor cells, micrometastasis, macrometastasis)

Also collected will be procedure related data including transit time to axilla from time of injection, size of tumor, location of tumor, tumor histology, breast size, patient age, BMI.

Consent:

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. The formal consent of a subject, using the IRB-approved consent form, will be obtained before that subject is submitted to any study procedure. Consent will be obtained by the study coordinator or investigator of the study in the breast clinic on Main Campus at Cleveland Clinic. Consent will be documented in the medical record.

Finance:

There are no additional costs to the patients. Mitaka USA will provide the PDE neo camera and ICG kit.

Funding Source:

CCF Breast Services Division

4.0 REGISTRATION

All patients enrolled on study will be entered into the Oncore database.

5.0 ADVERSE EVENTS AND REPORTING REQUIREMENTS

Adverse Events and Data Monitoring Committee (DMC):

Although we do not anticipate any adverse events, should any unexpected event occur, we will report the event in a timely manner per IRB policy. A DMC will not be used during this study.

6.0 DATA REPORTING/REGULATORY CONSIDERATIONS

Quality Control and Quality Assurance:

The study coordinator will be responsible to keeping data confidentially documented and reported in compliance with HIPAA and any other applicable regulatory requirements. The data will be kept for approximately 2 years after study completion, and will be accessible only to study staff.

Ethical Considerations:

This study will be conducted according to US and international standards of Good Clinical Practice for all studies. Applicable government regulations and Cleveland Clinic research policies and procedures will also be followed.

This protocol and any amendments will be submitted to the Cleveland Clinic Institutional Review Board (IRB) for formal approval to conduct the study. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator.

7.0 STATISTICAL CONSIDERATIONS

Sample size:

The study will be designed to determine whether ICG based axillary sentinel lymph node biopsy yields a similar number of nodes as ^{99m}Tc sulfur colloid lymph node biopsy. While SLN identification using ^{99m}Tc sulfur colloid is a common technique, neither of the two methods used in this study can be assumed to identify the "correct" set of nodes as sentinel. Therefore, for the purposes of this study, the sentinel status of a node will be defined as being flagged as sentinel by either one or both of the ICG or ^{99m}Tc methods. By this definition, sentinel nodes identified by ^{99m}Tc but not ICG are an error by omission for the ICG method and nodes flagged by ICG but not ^{99m}Tc are an error by the ^{99m}Tc method.

Let A be the number of Tc-positive and ICG-positive SNs detected, B be the number of Tc-positive and ICG-negative SNs detected, and C be the number of Tc-negative and ICG-positive SNs detected. The total number (N) of SNs detected is therefore $N = (A + B + C)$; the proportion of SNs (P_{Tc}) detected by the Tc method is $(A + B)/N$; and the proportion of SNs (P_{ICG}) detected by the ICG method is $(A + C)/N$.

As significant differences in the numbers of nodes identified by each method would have implications regarding the safety of ICG as a radiotracer, the null hypothesis is that the two methods identify an equivalent nodes of nodes as being sentinel nodes. Here equivalence is defined as the difference in the proportions of nodes flagged between the ^{99m}Tc and ICG methods falling within an interval $(-\delta, +\delta)$, where δ is taken to be 5%. Formally the null hypothesis for equivalence is:

$P_{ICG} - P_{Tc} < -\delta$ and $P_{ICG} - P_{Tc} \geq +\delta$

If the null hypothesis is rejected we may concluded for the hypothesis of equivalence that:

$\delta < (P_{ICG} - P_{Tc}) < \delta$

The equivalence hypothesis can be transformed into two one-sided hypotheses:

(A)

that the difference between the proportions is beyond the lower equivalence margin: null hypothesis A: $P_{ICG} - P_{Tc} < -\delta$, which, if rejected, permits the conclusion $P_{ICG} - P_{Tc} \geq -\delta$

(B)

that the difference between the proportions is greater than the upper equivalence margin: null hypothesis B: $P_{ICG} - P_{Tc} \geq +\delta$ which, if rejected, permits the conclusion $P_{ICG} - P_{Tc} \leq +\delta$.

Hypotheses A and B will be tested by comparing a two-sided 90% confidence interval (CI) for the difference in the proportions of SNs flagged by the two methods, with the 5% equivalence region ($-\delta, +\delta$). Tests for equivalence will be based on the methods for analyzing clustered paired binary data described in Obuchowski(13). To conclude for equivalence the 90% CI needs to be contained entirely within the defined equivalence region, which is equivalent to both null hypotheses (A) and (B) being rejected.

To estimate the number of SNs that will need to be examined, we assumed a detection rate $(A + B)/N$ of 97% for the Tc method, a discordance rate between the two methods $(B + C)/N$ of 6%, and set δ at 5%. We found through simulation that **255 SNs** will give adequate power (>80%) to demonstrate equivalence between the two methods, with a type I error (α) rate of 5%. This is estimated to require ~130 patients as the average SN yield is expected to be approximately 2 per patient.

8.0 REFERENCES

1. Nimura H, Narimiya N, Mitsumori N, et al. Infrared ray electronic endoscopy combined with indocyanine green injection for detection of sentinel nodes of patients with gastric cancer. Br J Surg. 2004;91:575–9.

2. Miyashiro I, Miyoshi N, Hiratsuka M, et al. Detection of sentinel node in gastric cancer surgery by indocyanine green fluorescence imaging: comparison with infrared imaging. Ann Surg Oncol. 2008;15:1640–3.

3. Kusano M, Tajima Y, Yamazaki K, et al. Sentinel node mapping guided by indocyanine green fluorescence imaging: a new method for sentinel node navigation surgery in gastro-intestinal cancer. Dig Surg. 2008;25:103–8.

4. Fujiwara M, Mizukami T, Suzuki A, Fukamizu H. Sentinel lymph node detection in skin cancer patients using real-time fluorescence navigation with indocyanine green: preliminary experience. J Plast Reconstr Aesthet Surg. 2008

5. Tsujino Y, Mizumoto K, Matsuzaka Y, et al. Fluorescence navigation with indocyanine green for detecting sentinel nodes in extramammary Paget's disease and squamous cell carcinoma. J Dermatol. 2009;36:90–4.

6. Gioux et al. "Image-Guided Surgery using Invisible Near Infrared Light: Fundamentals of Clinical Translation." Mol. Imaging 9(5): 237, 2011.

7. Tong et al. "Use of Fluorescence Imaging in Combination with Patent Blue Dye versus Patent Blue Dye Alone in Sentinel Lymph Node Biopsy in Breast Cancer." Journal of Breast Cancer. 17(3):250, 2014.

8. Chi et al. "Use of Indocyanine Green for Detecting the Sentinel Lymph Node in Breast Cancer Patients: From Preclinical Evaluation to Clinical Validation." PLOS One. 8(12): e83927, 2013.

9. Wishart et al. “A Feasibility Study of ICG Fluorescence Mapping for Sentinel Node Detection in Early Breast Cancer.” EJSO. 38: 651, 2012.

10. Sugie, T et al. “Comparison of the ICG Fluroscence and Blue Dye Methods in Detection of Sentinel Lymph Nodes in Early Stage Breast Cancer.” Ann Surg Onc. 20: 2213, 2013.

11. Ballardini, B. et al. “The ICG Method is Equivalent to the 99Tc-Labeled Radiotracer Method for Identifying the Sentinel Node in Breast Cancer: A Concordance and Validation Study.” EJSO 39: 1332, 2013.

12. Korn et al. “ING SPY Elite-Assisted Sentinel Lymph Node Biopsy in Cutaneous Melanoma.” Plast Recontr Surg. 133:914, 2014.

13. Obuchowski, NA. On the Comparison of Correlated Proportions for Clustered Data. Stat Med 1998 Jul 15;17(13): 1495-507.

14. Samorani et al. “The use of indocyanine green to detect sentinel nodes in breast cancer: A prospective study.” EJSO. 41: 64, 2014.