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Last Modified: May 3, 2019

Last Human Subjects Review: December 27, 2018

BMJ OPEN

Feasibility of Preoperative Tattooing of Percutaneously Biopsied Axillary Lymph Node: A Quasi Experimental Pilot Study

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Abstract

Introduction: Breast cancer is the leading cause of cancer mortality among females. Sentinel lymph node biopsy helps avoid axillary lymph node dissection and the associated morbidity. However, its utility is unclear in patients with biopsy proven axillary disease that has been treated with neoadjuvant chemotherapy. The objective of our study is to evaluate a) the feasibility of a novel technique of preoperatively tattooing suspicious lymph nodes with India ink, their intraoperative identification and retrieval (Phase I) and b) the application of this technique in patients who undergo neoadjuvant chemotherapy (Phase II).

Methods and Analysis: A quasi-experimental pilot study will be conducted to evaluate the feasibility of tattooing suspicious lymph nodes with sterile black India ink. The study will be conducted in two phases, with the second phase conditional upon the successful results of the first. In Phase I, only 10 patients who are committed to undergo upfront surgery (without neoadjuvant chemotherapy) will be included. These patients will have the suspicious lymph node tattooed by injecting India ink at the time of core needle biopsy. Intraoperatively, the axilla will be inspected to determine whether India ink tattooed in the lymph nodes can be visualized by the surgeon. Microscopic inspection for the presence of the dye in nodes retrieved by sentinel biopsy and/or axillary dissection will also be done. In Phase II, this process will be repeated for patients who undergo surgery after neoadjuvant chemotherapy.

Ethics and Dissemination: Ethical approval was obtained from the Aga Khan University Ethical Review Board (ERC# 2018-0345-1105). The process of sentinel node biopsy is a safe and routinely performed procedure at our institution. Intradermal injection of methylene blue can lead to skin necrosis; intra-parenchymal injection can cause induration and erythema with associated pain. These side effects can be minimized by diluting methylene blue which will be done. The complications that can result from all additional steps of study procedures will be discussed with the patient and their full responsibility will be borne by the institution. Although sterile black India Ink is safe to administer but possible side effects can include mucosal inflammation due to spillage of the ink, abscess formation and others such as an allergic reaction. If any of these situations are encountered full responsibility to treat the side effects will be borne by the study team using departmental funds. No dissemination plan has been identified at the time of writing of this protocol.

ClinicalTrials.gov Identifier:

Keywords: *Lower Middle Income Countries, Axillary Lymph Node Dissection, Sentinel Lymph Node Biopsy, Neoadjuvant Chemotherapy, and De-Escalating Surgery, Preoperative Tattooing of the Biopsied Lymph Node, Black or India Ink*

Strengths of Study

- Robust measures will be employed as trained and credentialed surgeon, radiologists and pathologists will perform the procedures and assess the outcomes.

Limitations of Study

- This will be a single institutional study, so generalizability will be limited.
- Sample size is small, but we are doing a pilot study to evaluate the efficacy of sterile black India ink.
- This study will be conducted only on female patients; breast cancer is rare in males, we will not be able to report the efficacy among male patients.

Background

Based on GLOBOCAN estimates, 18.1 million new cancer cases and 9.6 million cancer deaths were reported worldwide in 2018. Female breast cancer constituted 11.6% of the cancer burden, second only to lung cancer (1). The current treatment of breast cancer involves various combinations of multiple treatment modalities including surgery, radiation and systemic therapy. Traditionally, regional lymph node status was thought to be the most important determinant of the extent of surgery and need for systemic and radiation therapy (2). Axillary lymph node dissection (ALND) is, however, associated with significant morbidity (lymphedema, pain and decreased range of motion postoperatively). Sentinel lymph node biopsy (SLNB) has become the standard of care in clinically node negative (cN_0) early breast cancer (EBC) due to low false negative rates, without worsening of local control or survival (3) (4). This less extensive staging procedure has allowed safe omission of ALND in approximately 60% of patients with no pathological evidence of disease in the excised sentinel lymph node (SLN) (5).

Recent clinical trials have focused on further de-escalating surgery and have demonstrated that in patients with limited axillary disease (i.e. those with micro or macro-metastasis in <3 axillary lymph nodes) who undergo breast conservation and receive adjuvant systemic therapy and/or radiation, routine ALND may be safely omitted without impacting survival and maintaining the rate of local recurrence to <1% (6).

In locally advanced breast cancer with cN0 axilla, performance of SLNB after neoadjuvant chemotherapy (NCT) is now the standard of care. However, for patients undergoing NCT who demonstrate pathological evidence of disease in the axilla before commencing treatment, an ALND after completion of NCT has been the standard of care despite its associated morbidity. Inspired by the possibility and success of less surgery on the axilla in EBC, several studies have assessed the application of SLNB after NCT to patients with pathologic evidence of disease in the axilla at initial presentation (7). However, management of the axilla in such patients remains controversial (8). A trial by American College of Surgeons Oncology Group (ACOSOG) Z1071 evaluating the efficacy of SLN biopsy compared to ALND in cN+ patients who underwent NAC reported a false negative rate of 12.6% for SLNB which was higher than the pre-set acceptable rate of 10%. Additionally, the false negative rate was dependent on the number of lymph nodes retrieved, with 3 nodes being the number leading to an acceptable FNR of <10%. However, the retrieval of 3 SLNs cannot be guaranteed in the procedure regardless of currently used single or dual tracer technique thus making it impractical. Thus the utility of SLNB remains limited after an axilla is rendered clinically node negative by NCT due to a high false negative rate, unless at least 3 SLNs are recovered (9) (10).

In an attempt to lower the false negative rate of SLN in cN+ disease after NCT, preoperative tagging of the biopsied lymph node to facilitate retrieval has been evaluated (11). A study from MD Anderson evaluated the feasibility of marking a percutaneously biopsied lymph node with a clip at the time of core needle biopsy, followed by ultrasound guided placement of radioactive iodine-125 seed into this clipped node to facilitate identification and retrieval intra-operatively. The results showed a false negative rate

of 4.2% (95% CI, 1.4 to 9.5) when the clipped node was retrieved along with sentinel lymph nodes and 10.1% when SLNs alone were retrieved without the clipped node (95% CI, 4.2 to 19.8). Furthermore, 25% of the time the clipped node was not a sentinel node and would have been missed if targeted retrieval had not been performed (8). While the study showed promising results the technique requires a sonographically visible bio-resorbable polymer (HydroMark T3) and a separate procedure for placement of radioactive iodine-125 seeds limiting application (2) (12) (13) (14) (15).

Thus, alternative methods need to be identified for marking the percutaneously biopsied lymph node at the time of core needle biopsy. One recent study that evaluated the feasibility of tattooing axillary lymph nodes with black ink before NAC identified that the black ink was visible in 93% of the patients intraoperatively, and lasted for almost 7 months in cases where lymph node retrieval was performed after NCT (14, 16). This concept is adopted based on the successful experience in gastroenterology where tattooing is widely used for marking lesions or tumors biopsied during endoscopy as the tattoo ink can remains identifiable over a long period of time (17).

There is thus a need to identify and test techniques that are practical, limit the number of procedures performed and could help limit the extent of surgery without negatively impacting outcomes. For the patient undergoing neoadjuvant chemotherapy with biopsy proven disease in the axilla, this could be achieved by developing a technique that allows marking, identification and retrieval of the biopsied lymph node, after completion of NCT at the time of SLNB. Retrieval of this previously biopsied lymph node along with SLNs, if found to be representative of the status of the remainder of the axilla, could potentially eliminate the need for routine ALND and thus limit morbidity.

To the best of our knowledge this will be the first study conducted to evaluate the feasibility of tattooing and retrieval of suspicious lymph nodes using India ink. The primary objective of our study is to evaluate whether sterile black India ink, injected percutaneously into the biopsied lymph node, can be visualized intraoperatively (Phase I). The secondary objective is to determine whether the injected India ink remains

visible at the time of surgery even after neoadjuvant chemotherapy (lag time) and is the status of sentinel and tattooed lymph nodes predictive of the axillary nodal status.

Study Objectives

Primary Outcomes

- Intra-operative identification of tattooed lymph node(s) in upfront surgery group (Phase I)
- Intra-operative identification of tattooed lymph node(s) in the post-neoadjuvant surgery group (Phase II)

Secondary Outcome

- Concordance rate between identified sentinel node(s) and tattooed lymph node(s)

Methodology

Study Design

A quasi-experimental pilot study will be conducted to evaluate the feasibility of tattooing suspicious lymph nodes with sterile black India Ink in breast cancer patients. Patients with suspected (who have not had a breast biopsy yet but clinically are suspected to have breast cancer) or biopsy proven breast cancer, with clinically suspicious axillary nodes, who have not had axillary lymph node biopsy yet, will be considered for this study. Such patients will then undergo an ultrasound guided core needle biopsy of the breast (if not already done) as well as of the suspicious axillary lymph node, in the radiology department by study radiologists as per our current institutional protocol. For the purpose of the study, at the time of the lymph node core biopsy, the biopsied node will be tattooed by injecting 0.1-0.5 ml (larger lymph nodes will be injected with more ink) of sterile black India ink.

In the first phase, 10 patients planned for upfront surgery will be included. This part of the study will help to evaluate whether black India ink (injected percutaneously into the lymph node at the time of percutaneous axillary biopsy) can be identified intraoperatively by the surgeon and does it help in retrieval of this percutaneously biopsied lymph node. All lymph nodes excised including sentinel, tattooed (if recovered) and non-sentinel will be submitted in separately labelled containers for further

pathologic evaluation. Determination of concordance between sentinel and tattooed nodes, will be primarily done visually by the surgeon and confirmed by 2 independent pathologists, blinded to each other's findings. Pathologic evaluation will determine concordance between sentinel/tattooed and non-sentinel nodes.

In Phase 2, we will perform the same procedure as detailed above (percutaneous lymph node biopsy and tattooing of lymph node with black India Ink) on 30 patients who are planned to undergo neoadjuvant chemotherapy. Chemotherapy typically is administered over 4-6 months, which leads to a lag time between percutaneous lymph node biopsy/tattooing and surgery. We will need to determine whether the tattoo on the lymph node remains intraoperatively visible and retrievable despite the lag of several months (while undergoing neoadjuvant chemotherapy). Pathologic evaluation will determine concordance between sentinel/tattooed and non-sentinel nodes.

Clinical stage and evaluation by the surgeon as well as patient preference will determine the timing of surgery, upfront or after NCT. In all cases, whether pathologically negative or positive on biopsy, a SLNB will be performed at the time of definitive surgery, with dual tracer technique using technitium-99 sulfur colloid and methylene blue as per current institutional protocol. Intraoperatively, the axilla will be inspected to determine whether the black India ink tattooed in the lymph nodes can be visualized or not, is it easily distinguishable from methylene blue and is the tattooed lymph node also the SLN. In cases where biopsy of lymph node was negative, an intraoperative frozen section will be performed on the retrieved lymph nodes (SLN and tattooed) and need for ALND will be determined according to current institutional protocol. All those with evidence of metastatic disease on previous core biopsy or on frozen section of SLN/tattooed LN will then proceed to have an ALND. All lymph nodes i.e. sentinel, tattooed and non-sentinel (retrieved in ALND) submitted will be processed and evaluated as per routine protocol by a single study pathologist, who will issue the final pathology report. The additional study part will require evaluation of methylene blue and India Ink tattoo by the second independent study pathologist, to see if the two are grossly and/or microscopically distinguishable. Both pathologists will be blinded to each

other's findings. This additional evaluation will not affect the pathologic stage or further treatment decisions. This step/part of the study could however impact future surgical technique.

Study Setting

The study will be conducted at Department of Surgery in collaboration with Department of Pathology and Radiology, the Aga Khan University Hospital Karachi-Pakistan (AKUH). AKUH is a Joint Commission International Accreditation (JCIA) accredited hospital and is one of the biggest private tertiary care hospitals in Karachi. The multidisciplinary AKUH breast surgery team consists of well qualified breast surgeons, radiologists, medical oncologists and pathologists who provide evidence based standard care to breast cancer patients following strict adherence to institutional guidelines. The reason for conducting single center study is to limit variability in management of breast cancer patients at different centers as AKUH provides a non-biased, controlled environment to evaluate the feasibility of injecting sterile black India ink and subsequently retrieval of the SLN using dual tracer technique, with attempted identification and retrieval of the marked/tattooed lymph node.

Study Participants

Women greater than 18 years old with histologically confirmed diagnosis of breast cancer or clinically suspected breast cancer and clinically suspicious ipsilateral axillary lymph nodes (on clinical exam or ultrasound) presenting to AKUH fulfilling our eligibility criteria and willing to give written informed consent for the whole duration of study period will be recruited.

Eligibility Criteria

Inclusion Criteria

- Female greater than 18 year of age

- Breast cancer patient (biopsy proven or clinically suspected) with clinically suspicious (palpable on clinical exam or abnormal by ultrasound criteria but not biopsied yet) ipsilateral axillary lymph node(s). The ultrasonographic examination will be considered suspicious for metastasis if one or more of following criteria are present: 1. Eccentric cortical enlargement (>3 mm) or lobulation with displacement of hilum 2. Absent hilum and irregular border and hypoechoic echotexture 3. Spherical node 4. Perinodal vascularity. (18-20)
- Participants willing to undergo axillary lymph node percutaneous biopsy with marking/tattooing of the biopsied lymph node at Aga Khan University Hospital
- Participants intending to have definitive surgery at Aga Khan University Hospital

Exclusion Criteria

- Participants with terminal disease like renal failure will be excluded because these conditions can have profound effect on their course of treatment
- Participants with distant metastases
- Participants with prior breast or axillary surgery
- Participants with bilateral breast cancer, and those who have already had an axillary core needle biopsy prior to inclusion (to avoid a second procedure for tattooing)
- Participants with recurrent breast malignancy because their course of treatment might be different
- Participants that were initially suspected to have breast cancer, but pathology results did not confirm the diagnosis
- Pregnant and lactating women
- Men with breast cancer

Sampling Strategy

The study participants will be recruited through purposive sampling technique from a population of female patients, presenting to AKUH with biopsy proven or suspected breast cancer with a clinically suspicious lymph node in the ipsilateral axilla.

Sample Size Assumption

The sample size assumptions were based on reported proportion of correctly identified marked/tattooed lymph of 93% (14), with confidence level of 95% and design effect of 1, the minimum sample size calculated is 100 breast cancer patients. Since we are conducting a small feasibility pilot study, it will be conducted on 40% of the calculated sample size, i.e. on 40 breasts cancer patients with clinically suspicious, percutaneously biopsied and tattooed ipsilateral axillary lymph node. The sample size was calculated through Open-EPI version 3.01.

The first 10 participants will be those with clinically suspicious nodes having undergone a core needle biopsy with simultaneous injection of India Ink and now planned for upfront surgery. The next 30 patients enrolled will be those who are planned for NCT, regardless of the pathologic results of the axillary core needle biopsy. Since surgery in these 30 patients will be deferred for approximately 6 months, it will allow us to know if delayed retrieval of the tattooed lymph node is possible after NCT.

Study Procedure

Female patients with histologically confirmed diagnosis of breast cancer or clinically suspected breast cancer with clinically suspicious ipsilateral lymph nodes (not biopsied yet) will be approached to participate in our study by the research team. Consent from patients will be obtained by those who meet the inclusion criteria and intend to have surgical treatment at AKUH.

Participants as per the institutional guidelines will undergo the routine clinical breast examination by trained specialist breast surgeon and radiological investigation. Those with suspected or histologically confirmed breast cancer and suspicious (but not biopsied yet) ipsilateral axillary lymph nodes on clinical exam or ultrasound will undergo an ultrasound guided core needle biopsy of the breast as well as the single, most

suspicious axillary lymph node either concurrently with core biopsy of the breast or in addition to previously performed core needle biopsy of breast, in the radiology department by study radiologists.

The biopsied lymph nodes will be tattooed with sterile black India ink immediately following sampling of the suspicious lymph node. Those planned for upfront surgery (Phase I) will be prepared and consented for surgery. Those planned for NCT (Phase II) will receive NCT followed by definitive surgery after completion of chemotherapy.

All study patients will have a sentinel lymph node biopsy and frozen section on retrieved SLN as part of axillary surgery. For this purpose after injection of TC^{99} and lymphatic mapping preoperatively, diluted methylene blue will be injected into the subareolar plexus intraoperatively. The axillary hot spot will be assessed and documented for presence or absence, using a gamma probe. Intraoperatively axilla will be inspected to determine whether sterile black India ink tattooed in the lymph nodes is visible or not. Sentinel lymph node biopsy will be performed in usual fashion including identification of palpable lymph nodes. Total number of sentinel lymph nodes retrieved, number of hot, number of blue and number of hot and blue will be documented. If the sentinel node is also the marked/tattooed node it will be assessed and documented.

Subsequently, those with a biopsy proven axillary metastatic disease on axillary core needle biopsy (regardless of frozen section results), will proceed to have the planned breast procedure and axillary lymph node dissection levels I and II in usual fashion. Management of axilla in those participants who did not have biopsy proven metastatic disease on axillary core needle biopsy (but had a suspicious node leading to core biopsy), will be dictated by results of frozen section analysis. If the frozen section results show absence of metastatic disease in the submitted lymph nodes, no additional axillary surgery will be performed. While the frozen section is in process and results are awaited, the surgeon may proceed with the planned breast procedure. ALND will be followed by placement of a drain in the axilla as per routine.

For post NCT patients, extent of fibrosis (mild, moderate or severe) will be documented. All submitted lymph nodes will be evaluated by two independent pathologists to ascertain the visualization of sterile black

India ink within the nodes, and usual histologic assessment of all submitted specimens. Correlation between, marked/tattooed and sentinel nodes (including palpable) will be determined. Tumor pathology, including type, grade, receptors (ER, PR and Her-2/neu) will be reported. Credentialed surgeon, radiologists and pathologists according to institutional guidelines will participate in the study as this will lead to minimization of experimenter/assessor bias. (Study Flow Diagram)

Statistical Analysis

Analysis will be performed in Stata version 12. Descriptive analysis will be performed. For continuous variables either Mean± S.D or Median with IQR will be reported depending on the normality assumption of the variables. For categorical variables frequency with percentages will be reported. Proportion of lymph node visualized intraoperatively with Black India Ink will be reported. Concordance between the sentinel lymph nodes and tattooed biopsied lymph nodes will be reported. False negative rate (FNR) will be determined to assess the findings of preoperative pathological assessment against the final histological findings of the resected nodes and 95% Confidence interval (CIs) for FNRs will be calculated by exact method for the binomial proportion.

Ethical Considerations

Ethical approval is obtained Aga Khan University Ethical Review Committee no 2018-0345-1105. Written informed consent will be taken from the participants by properly trained data collectors. They will be explained the study procedures in detail along with the risks and benefits associated in taking part in the study. Data collectors will only ask to sign or stamp the consent form by the participants after they have understood the entire procedure. Data collectors will be trained by PI/Co-PI. Data collectors will be reinforced to recruit only those participants who will be willing to participate in the study. Participants will be allowed to leave the study at any point in time and they will continue to receive quality standard treatment services at AKUH. In addition all study materials containing personal identifiers will be kept in a locked

file cabinet. A unique study identification number will be assigned to each participant. After that data will be entered from hard copy into the electronic database that will be password protected and only accessed by the research staff of the study. Participants will be explained in detail regarding the risks associated with the procedure. Complications that can result due to additional steps of study procedures, their full responsibility will be borne by the institution. Although sterile black India ink is safe to administer but possible side effects can include mucosal inflammation, due to spillage of the ink, abscess formation and allergic reaction (17).

List of Abbreviations

Aga Khan University Hospital	AKUH
Lower Middle Income Countries	LMIC
Axillary Lymph Node Dissection	ALND
Sentinel Lymph Node Biopsy	SLNB
Clinically Node Negative	cN_0
Early Breast Cancer	EBC
Sentinel Lymph Node	SLN
Neoadjuvant chemotherapy	NCT
American College of Surgeons Oncology Group	ACOSOG
False Negative Rate	FNR
Joint Commission International Accreditation	JCIA
Standard Deviation	S.D
Interquartile Range	IQR
Confidence interval	CI
Principal Investigator/Co-PI	PI/Co-PI

Declarations Section

Ethics approval and consent to participate

Study protocol was approved by the Aga Khan University Hospital Ethics Review Committee (ERC) with ERC Ref 2018-0345-1105.

Consent for publication

Not applicable

Availability of data and material

As this is a study protocol, we do not any study related data or material to share.

Competing interests

All authors declare no competing interest

Funding

The study is funded by Department of Surgery, Aga Khan University Faculty Research funds

Authors' contributions

AKS conceived and designed the study and wrote the manuscript. WK and BA directly overlooked all aspects of study design and wrote the manuscript with AKS. IM, SA, MUT, RI, MU assisted as local experts and informed aspects of development of the study intellectually. All authors have contributed intellectually to this manuscript. All authors read and approved the final manuscript.

Acknowledgements

We would also like to acknowledge Dr. Monica Morrow for her critical feedback on the study design and protocol.

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