Microinvasive Technology for the Diagnosis and Staging of Breast Cancer

by

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SUMMARY

The purpose of this thesis was to evaluate microinvasive technology for the management of non-palpable mammographic findings with high risk for breast cancer. The specific objectives were, for the first part, to evaluate the Advanced Breast Biopsy Instrumentation System (ABBI) as a diagnostic and therapeutic tool for breast disease. For the second part, the objective was to evaluate lymphoscintigraphy with a malignancy specific radioactive agent (^{99m}Technetium Sestamibi) as a non-surgical staging tool for breast cancer.

Design:

The thesis consists of two observational studies. The first study was partially retrospective and partially prospective. The second study was prospective. The research was conducted between September 1997 and December 2001.

Methods:

For the first study 262 women with non-palpable mammographic abnormalities were enrolled. Of these, 260 women underwent an ABBI. The ABBI procedure was performed by 3 surgeons in two hospitals in Montreal. The files of 531 women with similar findings who underwent a wire localization excisional biopsy in the same hospitals by the same surgeons were retrospectively reviewed. Data obtained included technical success, macroscopic and microscopic clarity of margins, need

for supplemental surgery and residual cancer, volume of breast tissue excised, patient satisfaction, surgeon volume-performance association and health care costs.

For the second study, 110 women with confirmed operable primary breast cancer who required axillary lymph node dissection were enrolled. All the patients underwent two lymphoscintigraphies. The first (preliminary) lymphoscintigraphy took place at least 2 weeks before surgery and the second (preoperative) took place 2-24 hours before surgery. For the preliminary lymphoscintigraphy, 47 (42.7%) of the 110 women were tested with ^{99m}Technetium Sestamibi and 63 (57.3%) were tested with ^{99m}Technetium Sulphur Colloid. For the preoperative lymphoscintigraphy all patients were tested with ^{99m}Technetium Sulphur Colloid. All patients underwent axillary lymph nodes dissection. The data reviewed was the presence of metastasis in the axillary lymph nodes excised and the lymphoscintigraphy gamma camera imaging and gamma probe digital outcomes. The ROC curve was used to define the most probable cut-off points for the distinction between gamma counts representing positive and negative for metastasis axillary lymph nodes.

Results:

For the first study, diagnostic effectiveness of the ABBI was 99.6% and the mean volume of excised breast tissue was 40cc. No serious complications were reported. For wire localization, the diagnostic effectiveness was 98.0% and the mean volume of excised breast tissue

was 102cc. severity of complications was similar between the two techniques. The therapeutic effectiveness of the ABBI was 76.3%, supplementary surgery was required in 27.6% of the patients, and residual cancer was detected in 23.8%. The therapeutic effectiveness of wire localization biopsy was 47.0%, 53% of the patients underwent supplementary surgery and residual tumor was found in 48.0%. Of the 260 patients who underwent an ABBI, 51% reported a good level of satisfaction and 23% reported excellent. A significant association was shown between volume and therapeutic effectiveness for all 3 surgeons. On the average, the ABBI resulted in a cost reduction of $5,352 CAD (2000).

For the second study, the sensitivity of ^{99m}Technetium Sestamibi lymphoscintigraphy imaging was 50%, the negative predictive value was 83.8% and the proportion of false negative results was 17.1%. Logistic regression showed a statistically significant ($p<0.001$) association between the gamma probe counts and axillary lymph node metastasis. Using 3,080 counts as cut-off point on the ROC curve the sensitivity and false negative rate were 100%, the specificity was 94.3%, and the positive predictive value was 83.3%.

Conclusion:

The results of the first study show that the ABBI offers a safe and well tolerated microinvasive surgical technique, with superior therapeutic effectiveness, less invasiveness, and better cost effectiveness than wire

localization excisional biopsy. The strong volume-performance association shows that the therapeutic effectiveness of the ABBI can improve with proper training and experience.

The results of the second study show that ^{99m}Technetium Sestamibi lymphoscintigraphy imaging was 50% the negative predictive value was 83.8% and the proportion of false negative results was 17.1%. A significant association was shown between the intensity of radioactivity in the hot node as measured by the gamma-probe counts and the presence of axillary lymph node metastasis.

In conclusion, this thesis demonstrates that both the ABBI and lymphoscintigraphy with ^{99m}Technetium Sestamibi are superior to conventional techniques used for the management of mammographic abnormalities and specifically breast cancer. Proper training of surgeons in highly qualified training centers with a high volume of cases can help further improve the effectiveness and increase the practise of these techniques in Canadian hospitals. This may in turn increase the benefits for the patients and reduce the healthcare costs for the management of breast disease and specifically breast cancer in Canada.

RÉSUMÉ

Cette thèse est une combinaison de deux études observationnelles possédant une intention commune; l`évaluation de la technologie innovatrice microeffractive pour la gestion du cancer du sein. Les objectifs spécifiques étaient en premier lieu, d'évaluer `the Advanced Breast Biopsy Instrumentation System (ABBI)` comme instrument de diagnostique et de thérapie pour les maladies du sein (ou maladie mammaire) puis en deuxième lieu, d'évaluer lymphoscintigraphie avec un agent radioactif malin spécifique (99mTechnetium Sestamibi) comme outil de stadification non-chirurgical pour le cancer du sein. La recherche fut effectuée entre septembre 1997 et décembre 2001.

Design:

Cette these comprends deux études d'observations. La première étude est partiellement retrospective et partiellement prospective. La recherche a été exécutée entre septembre 1997 et décembre 2001

Méthodes

Pour la première étude 262 femmes avec des anomalies mammographies non-palpable ont été choisies. De celles-ci, 260 femmes ont subit un ABBI. La procédure ABBI a été effectué par 3 chirurgiens dans deux hôpitaux dans la région de Montréal. Les fiches de 531 femmes avec des résultats similaires et qui ont subit une biopsie excisionelle dans les mêmes hôpitaux et par les mêmes chirurgiens ont aussi été revisés. L'information obtenue inclus : succès de la technique, la marge

macroscopique et microscopique, besoin de chirurgie supplémentaire et cancer résiduel, volume de tissue du sein excisé, satisfaction du patient, association du volume-performance du chirurgien et les coûts de la santé.

Pour la seconde étude, 110 femmes avec un cancer du sein opérable et qui nécessitait une dissection des glandes lymphatiques auxiliaires ont été recrutées. Toutes les patientes ont subit deux lymphoscintigraphies. La première lymphoscintigraphie (préliminaire) a eu lieu au moins deux semaines avant la chirurgie et la seconde (pré-chirurgie) a eu lieu 2 à 24 heures avant la chirugie.

Pour la premiere lymphoscintigraphie, 47 (42.7%) des 110 femmes ont été testées en utilisant 99mTechnetium Sestamibi et 63 femmes (57.3%) ont été testées en utilisant 99mTechnetium Sulphur Colloid. Toutes les patientes ont été testées en utilisant 99mTechnetium Sulphur Colloid. Toutes les patientes ont subi une dissection des glandes lymphatiques auxiliaires.

La première partie de cette thèse démontrait que, pour la gestion des anomalies mammographiques qui ont un risque élevé d'avoir un cancer du sein, le procédé d'instrumentation avancé de biopsie du sein (cABBI) offre une efficacité thérapeutique supérieure, moins invasive, et moins coûteuse que le fil localisateur guidant la biopsie excisionnelle. De plus, il a été démontré que le procédé d'cABBI est sécuritaire et bien toléré par la plupart des patientes. La forte association volume-

performance démontre que l'efficacité du procédé d'cABBI augmentera si les chirurgiens reçoivent une formation adéquate.

La deuxième partie de la thèse démontrait que la lymphoscintigraphie avec le Technétium99m Sestamibi, lorsque pratiqué adéquatement, offre une technique très précise et non-invasive pour la détection de métastases au niveau des ganglions axillaires au stade primaire du cancer du sein. Cependant, ceci est vrai uniquement lorsque la sonde actuelle à détection gamma est utilisée. L'imagerie lymphoscintigraphique n'était pas précise pour la détection de métastases. Avec une formation adéquate et de l'expérience, l'implantation de la lymphoscintigraphie avec le Technétium99m Sestamibi pourrait aider à minimiser la morbidité associée à la dissection conventionnelle des ganglions axillaires. De plus, cela pourrait réduire la probabilité d'omettre des métastases.

En conclusion, les résultats de cette thèse démontrent que les techniques d'cABBI et de lymphoscintigraphie avec le Technétium99m Sestamibi peuvent toutes les deux aider à améliorer l'efficacité de la gestion actuelle des anomalies mammographiques et du cancer du sein. Une formation adéquate des chirurgiens pour ces deux techniques, dans des centres de formation très spécialisés avec un volume élevé de cas, pourrait aider à améliorer l'efficacité de ces techniques. Ceci pourrait augmenter les avantages liés au traitement pour les patientes et réduire les coûts des soins de santé pour la gestion de la maladie du sein et

spécifiquement le cancer du sein au Canada et dans d'autres régions du monde.

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STATEMENT OF ORIGINALITY

The two studies included in this thesis evaluate the effectiveness of a minimally invasive surgical diagnostic technique, the Advanced Breast Biopsy Instrumentation System (ABBI) and a non-surgical staging technique, lymphoscintigraphy, for the diagnosis and surgical treatment of breast cancer.

The ABBI has been evaluated previously. However, in the current study the following are important differences from previous studies. First, this is a prospective multi-center study with data from many surgeons; second, the outcome measures were ascertained by an observer that was not involved in conducting the procedure, thus minimizing bias. The evaluation of the association between surgeon experience and effectiveness or volume performance is an original contribution of the current study. The economic assessment and description of patient satisfaction within the Canadian Healthcare System are also original contributions of the current study.

Sentinel lymph node biopsy with the guidance of lymphoscintigraphy has been evaluated in other studies. The purpose of lymphoscintigraphy is first, to reveal, with the help of a radioactive agent, the lymphatic drainage pathway of the particular area of the breast where the cancer is located. Second, to guide the detection and the dissection of the first lymph node to potentially receive malignant or

benign tumor cells from the area of the breast where the tumor is located, called the sentinel lymph node. The current study evaluated the use of lymphoscintigraphy with ^{99m}Technetium Sestamibi, a malignant cell specific agent, to accurately detect axillary lymph nodes with metastatic invasion from the tumor in the breast area under investigation. This is an original contribution of the current study since this method has never been evaluated.

The thesis candidate conceived and designed both studies, was the author of the protocols, conducted all data collection, data analysis and reporting for both studies. The candidate also collaborated in modifications in the development of the ABBI. In addition the candidate will be responsible for the preparation and publication of manuscripts reporting the results of these two studies.

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PROLOGUE

This thesis presents two research projects that have a common goal; the evaluation of microinvasive techniques for the diagnosis and staging of breast cancer. The common underlying theme of these two projects is the use of minimally invasive or non-invasive procedures for the diagnosis and surgical management of breast cancer.

1 STATEMENT OF THE PROBLEM AND RATIONALE

1.1 INTRODUCTION

1.1.1 PROLOGUE

The purpose of the current chapter is to describe the current state of knowledge and to establish the rationale for the two studies included in this thesis. The chapter will be comprised of a brief review of the epidemiology of breast cancer and a description of the methods currently used for diagnosis, staging, and treatment of early breast cancer.

The use of microinvasive methods for the diagnosis and management of early breast cancer will be presented in comparison to alternative more conventional and invasive techniques. Finally, a review of the literature on the two techniques evaluated in the current thesis will be presented, thus defining the knowledge gap and establishing the need and rationale for the studies presented in this thesis.

The two techniques evaluated in this thesis have one main common characteristic; the use of microinvasive technology for the management of breast cancer. The first is a surgical technique that aims to accurately localize and excise breast tumors, which are detected in a mammogram but are too small to palpate, with the least possible excision of surrounding healthy breast tissue. The second involves the combination of radiolabelled isotopes along with an imaging, acoustic and digital technique. The aim is to detect axillary lymph node

metastasis from the cancer in the ipsilateral breast without the need for surgical excision of axillary lymph nodes. In essence the common goal of both techniques is to diagnose and manage breast cancer while minimizing surgical invasiveness without compromising patient care.

1.1.2 EPIDEMIOLOGY OF BREAST CANCER

In the last two decades, breast cancer is the most frequently diagnosed cancer in Canadian women, accounting for 30% of all cancer cases in women[1-4]. The number of new breast cancer cases diagnosed increased, rising from 10,175 in 1981 to an estimated 21,600 in 2005 (Figure 1)[3,5]. However, breast cancer mortality rates have declined steadily since 1993 (Figure 2)[3].

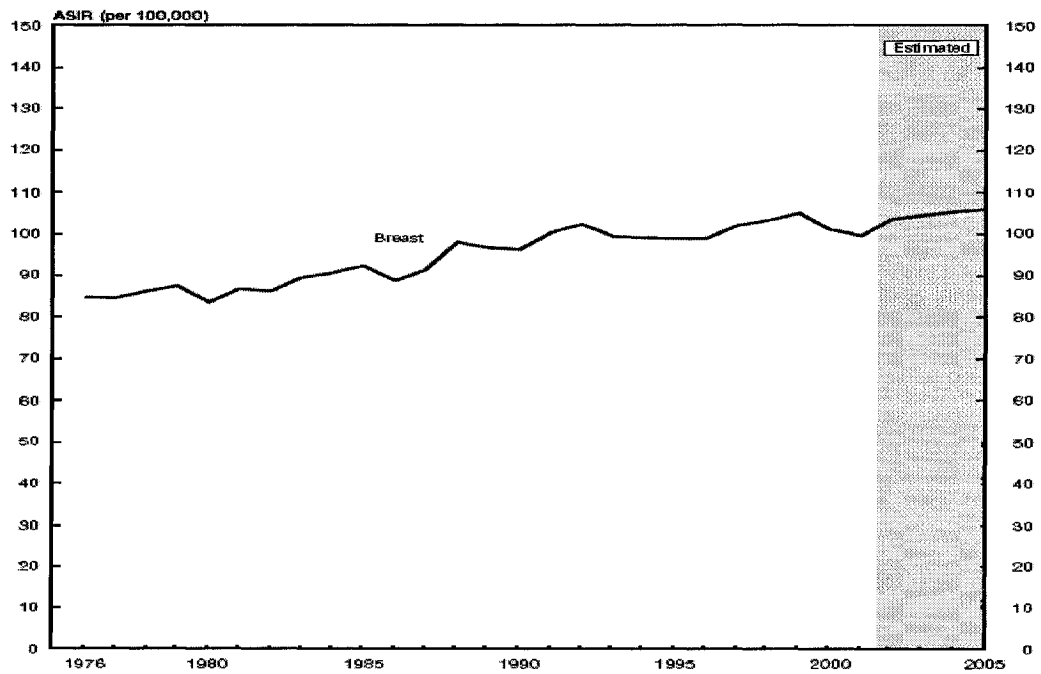


Figure 1: Age-Standardized Incidence Rates (ASIR) for Selected Cancer Sites, Females, Canada, 1976-2005, National Cancer Institute of Canada. Canadian Cancer Statistics, 2005.

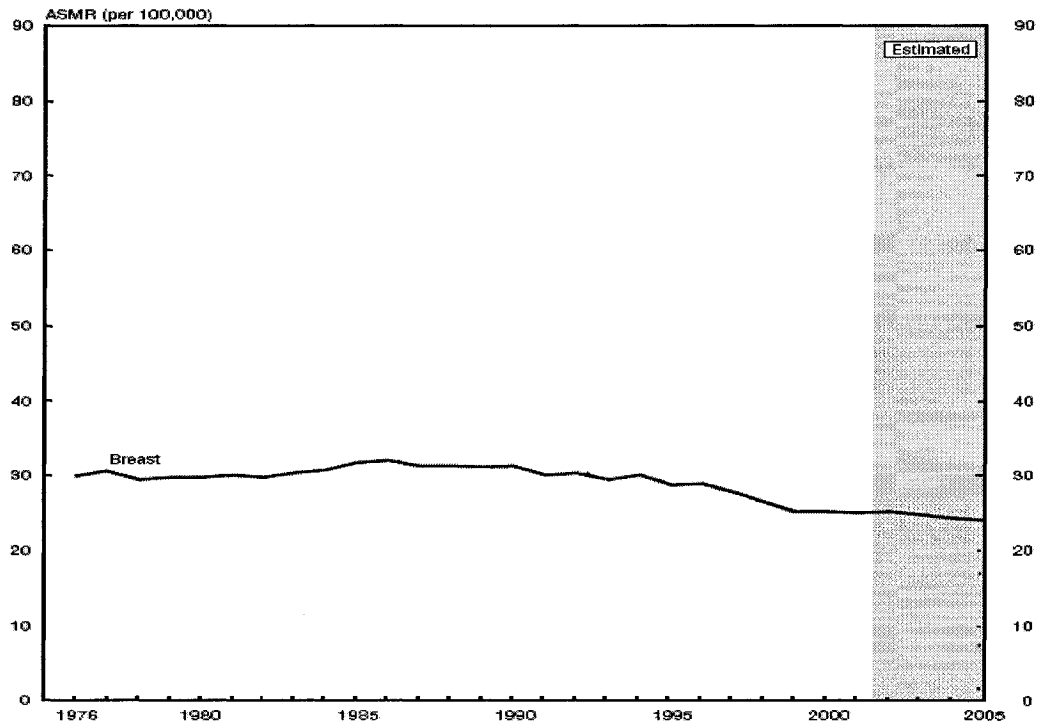


Figure 2: Age-Standardized Mortality Rates (ASIR) for Selected Cancer Sites, Females, Canada, 1976-2005, National Cancer Institute of Canada. Canadian Cancer Statistics, 2005.

According to Canadian Cancer Statistics, it is estimated that in 2005 approximately 21,600 women will be diagnosed with breast cancer and 5,300 will die because of this disease[3]. For the same year, approximately 150 men will be diagnosed with breast cancer and 45 will die because of the disease[3]. It is estimated that in 2005 an average of 415 Canadian women will be diagnosed with breast cancer each week and 102 Canadian women will die each week because of breast cancer[3].

Estimates for 2005 show that approximately 29% of breast cancers are diagnosed at 70 years of age or older, 50% between 50 and 69 years

and 21 % occur in women younger than 50 years of age[3]. Breast cancer at ages 20-49 is the most common cancer in women in this age group, with 4,520 new cases diagnosed of which 625 will die because of the disease (Figures 3 and 4)[3].

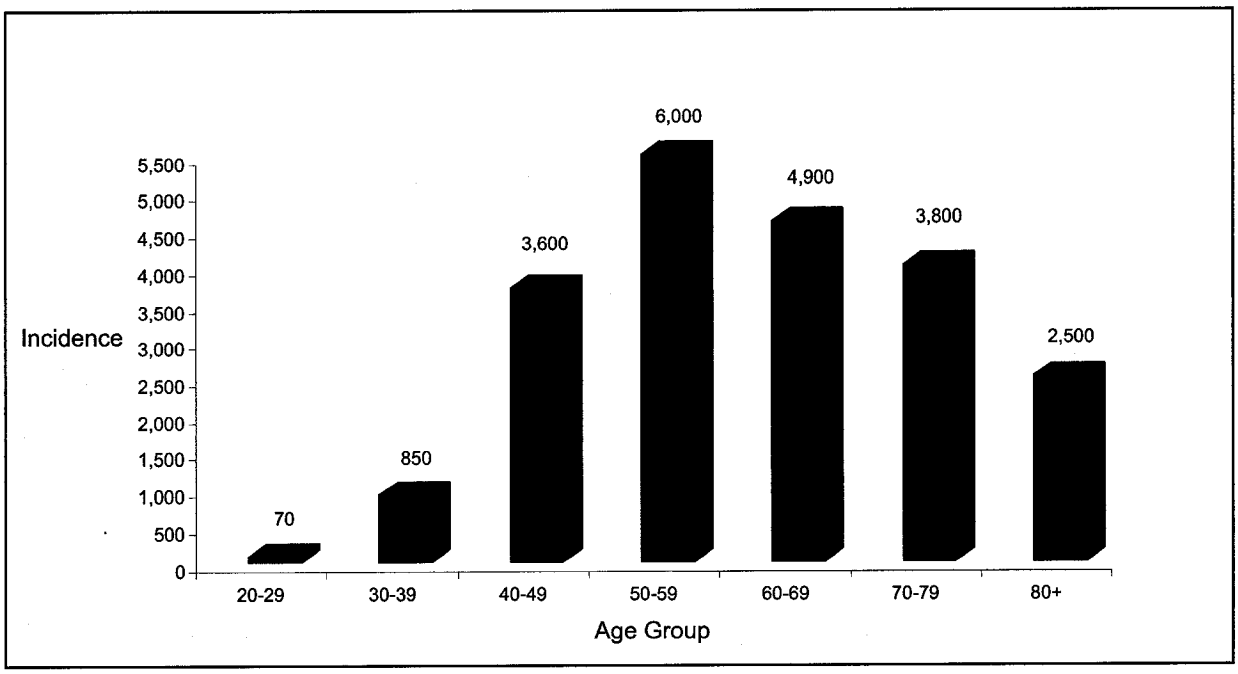


Figure 3. Distribution of Breast Cancer by Age Group in Canada, 2005

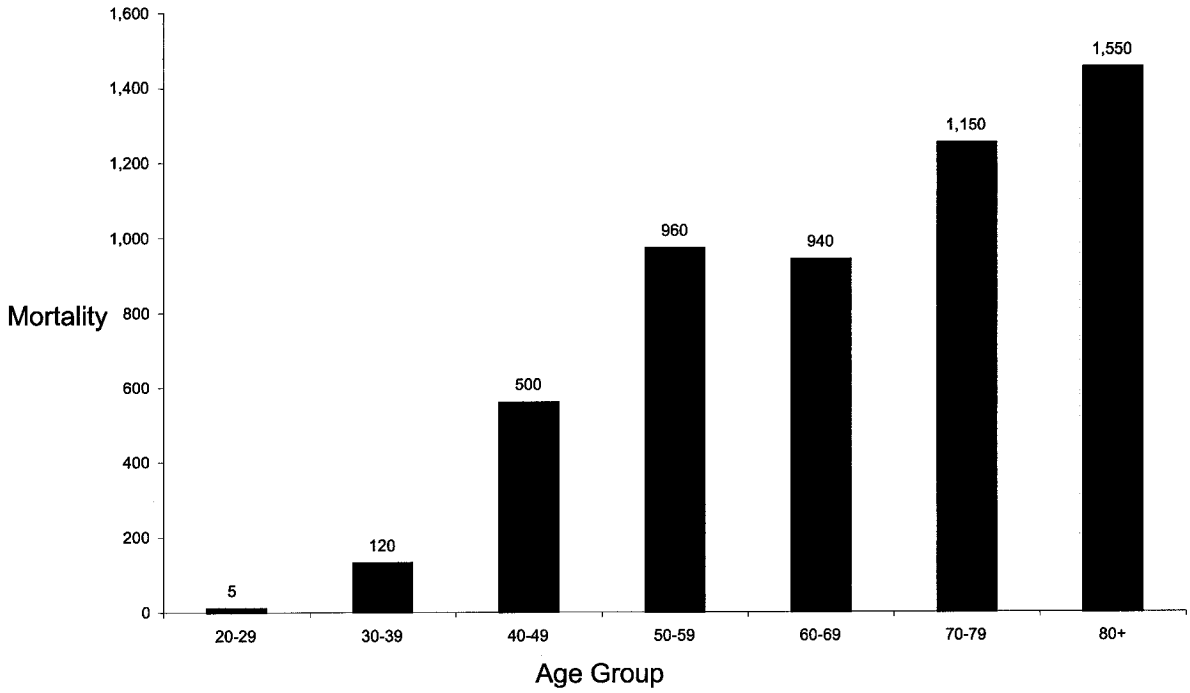


Figure 4. Mortality of Breast Cancer by Age Group in Canada, 2005

According to the World Health Organization, more than 1.2 million people will be diagnosed with breast cancer worldwide in 2005[6,7]. For the same year, the American Cancer Society estimates that approximately 211,240 women in the United States will be diagnosed with breast cancer[8,9]. An estimated 40,410 women and 460 men will die from breast cancer in the United States in 2005[8,9]. According to the American Cancer Society, the chance that breast cancer will be cause of death for a woman's is about 1 in 33 (3%)[9].

1.1.3 CLINICAL AND PATHOLOGICAL STAGING OF BREAST CANCER

The purpose of cancer staging is to determine the anatomical extent of the disease and the tumor's likelihood for metastasis in order to make decisions about the most appropriate treatment. For adequate staging of the disease, physical (clinical) findings and pathological data from the excised cancer must be combined.

The most common system used to describe the stages of cancers is the American Joint Committee on Cancer (AJCC) TNM system. This staging system classifies cancers based on both physical findings and the pathological assessment of the excised tumor and axillary lymph nodes (Appendix 1-3)[10]. The following classification scheme is used:

a. **T (0 – 4)** describes the tumor size and spread to the skin or chest wall under the breast. Higher T numbers indicate a larger tumor and/or wider spread to tissues near the breast.

b. **N (0 – 3)** indicates whether the cancer has spread to lymph nodes near the breast and, if so, how many lymph nodes are affected. The higher the number, the higher the level of lymph nodes invaded.

c. **M (0 – 1)** indicates whether the cancer has spread to distant organs or to lymph nodes draining any organ in the body other than the breast. Distant organs could be the liver, brain, and bones among others.

According to the 2002 American Joint Committee on Cancer (AJCC) TNM System there are five possible stage classifications (0, I, II, III, IV). Stage 0 tumors have the best prognosis and almost all are curable. Stage I cancers are localized to the breast and are small in size. Stage II is reserved for cases with regional lymph node metastasis and has a worse prognosis than I and 0 but better than III and IV. Stage IIIa denotes invasive breast cancer in which the tumor is larger than 5cm or the tumor has spread to lymph nodes, and the nodes are clumping or sticking to one another or surrounding tissue. Stage IIIb describes invasive breast cancer in which a tumor of any size has spread to the breast skin, chest wall, or intramammary lymph nodes. Stage IV cancers are generally non-treatable and involve distant metastases[10] (Appendix 4).

This study concentrates on early breast cancer because the ABBI is applicable only to tumors with a 2cm or smaller diameter. The TNM classification for early breast cancer is as follows:

a. **Stage 0** (Tis, N0, M0) refers to pre-invasive cancers (tumors in situ) that have yet to penetrate the basement membrane of the ductile or lobule. There are no regional or distant metastases.

b. **Stage I** (T1, N0, M0) refers to invasive tumors without metastases.

c. **Stage IIA** describes undetectable (T0, N1, M0) or small tumors with regional metastases (T1, N1, M0) or larger primary tumors without metastases (T2, N0, M0).

1.1.3.1 Prognostic Factors for Breast Cancer

Clinical characteristics that determine the prognosis of breast cancer are tumor size and location. The probability that breast cancer has metastasized is directly related to the size of the tumor. A metanalysis performed by Nemoto et al showed a strong association between increasing tumor size and probability of axillary node metastasis[11]. After reviewing published literature of a total of 12,981 patients, Nemoto reported that tumors of 0.1–10mm in diameter have a 24.7–28.6% probability of axillary metastasis compared to tumors 11–30mm where the probability of metastasis increases to 42.1%. Furthermore, tumors with a diameter greater than 31 mm have more than 50% probability of metastasis[11-13].

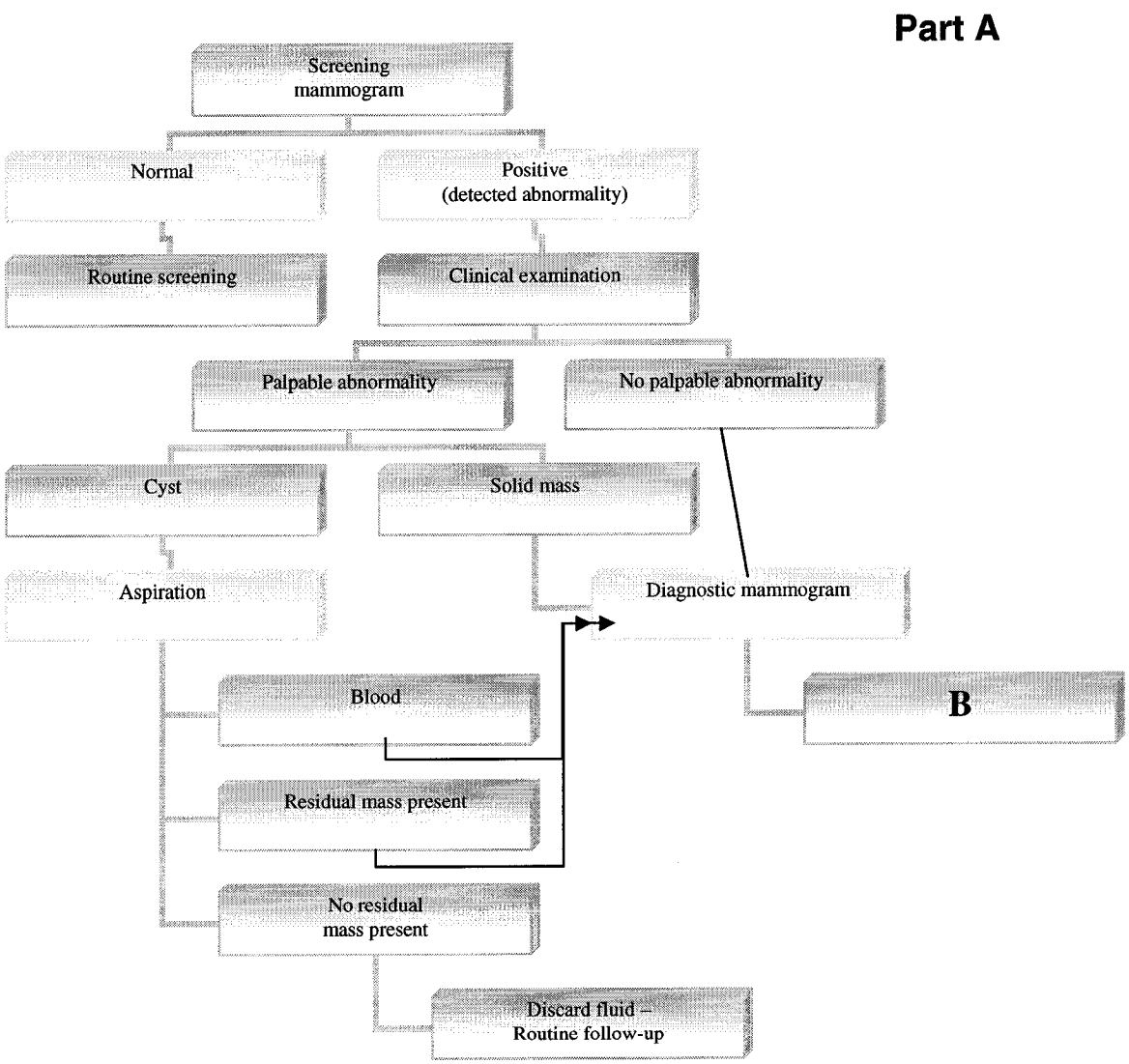
The location of the primary tumor has prognostic importance for tumors without axillary lymph node metastasis. While the risk for axillary lymph node metastasis is considered greater for lateral versus medial breast cancers, there are data suggesting that patients with medial tumors have a worse prognosis than those with lateral tumors due to an increased risk of local recurrence[11-19].

An additional prognostic factor is the presence and sensitivity of estrogen and progesterone receptors in the tumor. Absence of both estrogen and progesterone receptors has been associated with an increased risk for breast cancer recurrence due to resistance to anti-

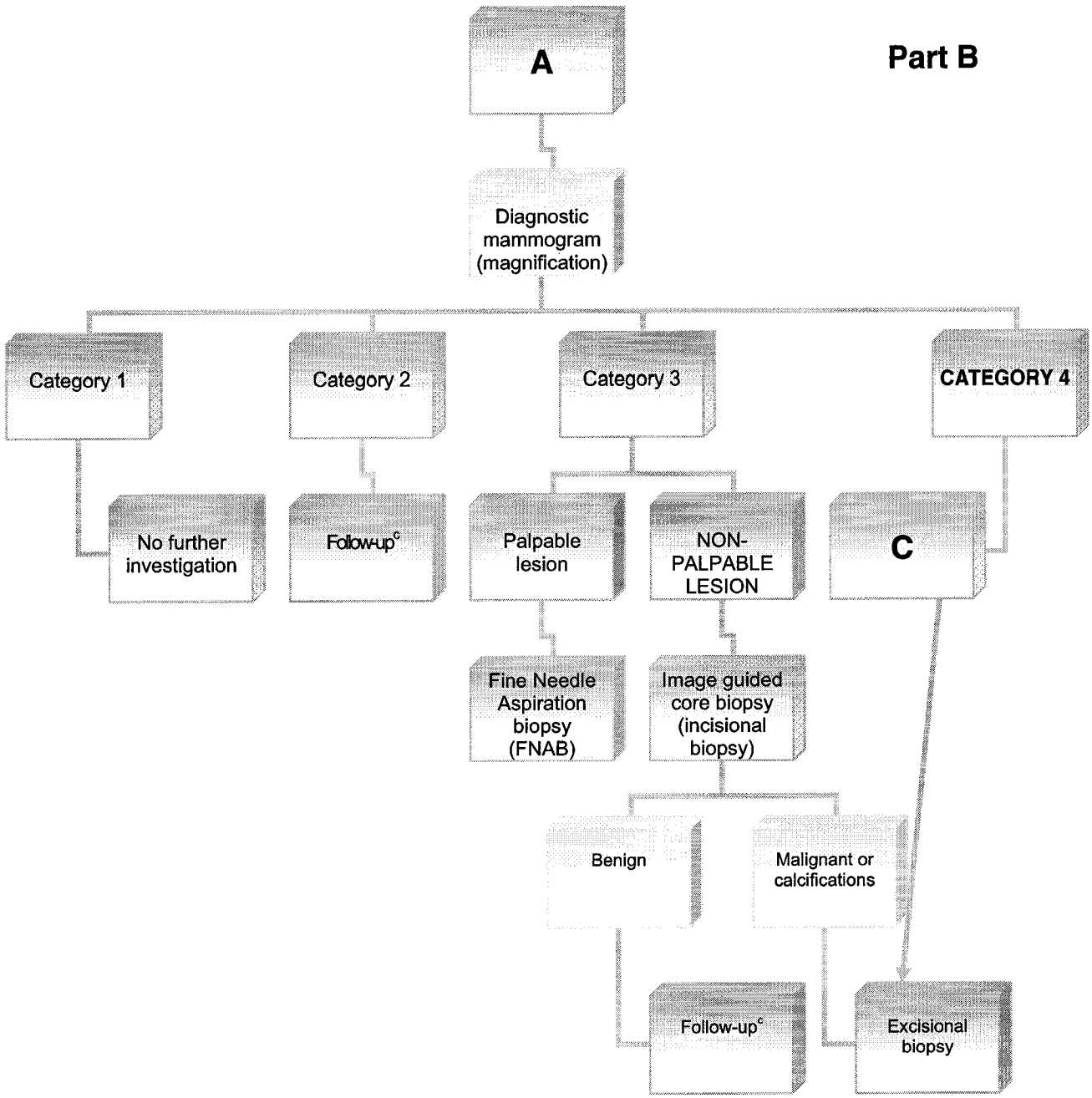
estrogen therapy. The status of hormone receptors is therefore useful in decision-making about hormonal anti-cancer therapy[18,19].

1.1.4 DIAGNOSIS AND MANAGEMENT OF BREAST CANCER

The diagnostic algorithms presented in Figures 5A-C are based on the Recommendations of the Canadian Steering Committee on Clinical Practice Guidelines for the Care and treatment of Breast Cancer[20].

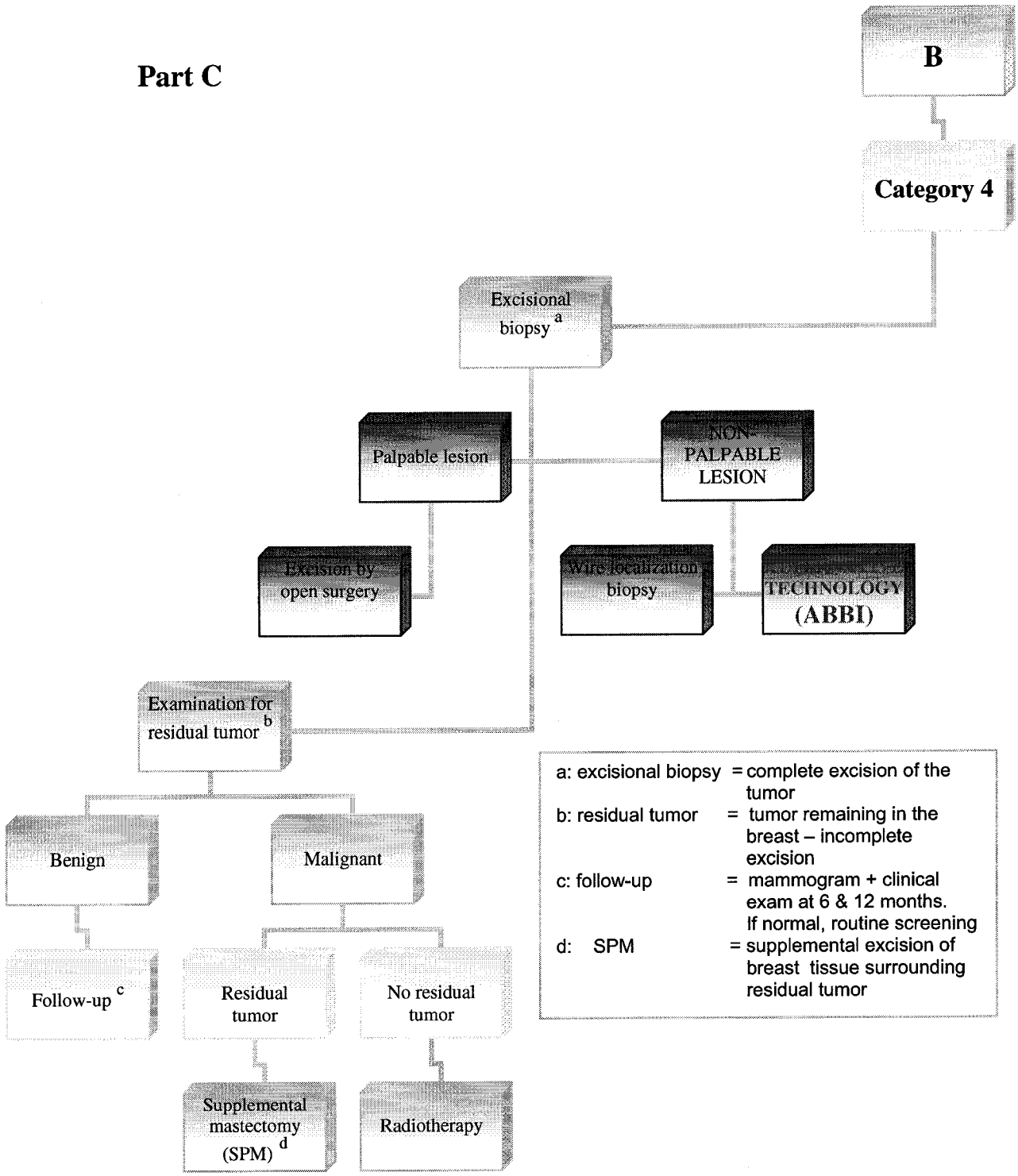


Figures 5A: Algorithm for the management of breast disease



Figures 5B: Algorithm for the management of mammographic finding

Part C



Figures 5C: Algorithm for the management of Category IV

Once an abnormality is detected on a screening mammogram it requires further investigation with clinical assessment and a higher sensitivity mammogram (diagnostic mammogram)(Fisure 5B). Clinical evaluation should include a medical history and complete examination of the breast, both axillae and the supraclavicular areas (Figure 6).

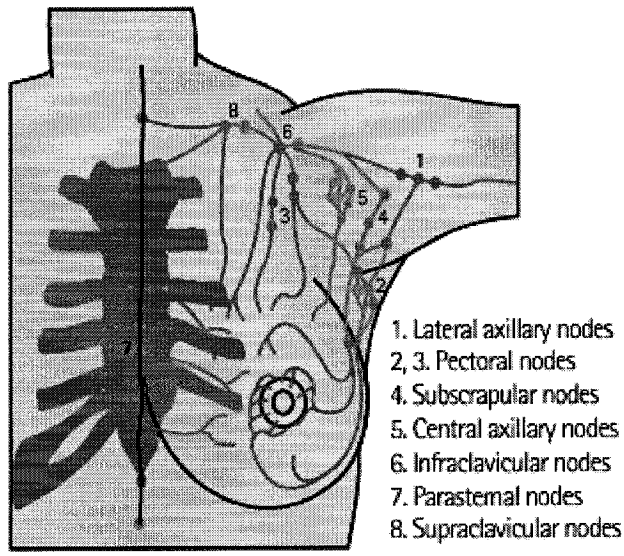


Figure 6: Lymphatic system serving the breast. Lamarque J-L, ed. Anatomy and embryology. In: An atlas and text of the breast: Clinical radiodiagnosis. London: Wolfe Medical Publications, 1984: 17-2821

The diagnostic mammogram should include a more detailed image of the abnormality with multiple views. If there is doubt or suspicion of malignancy additional imaging should be obtained with magnified views and spot compression of the area of interest (Figure 5B). Magnification offers an enlarged and more detailed image of the abnormal features and spot compression applies local pressure to displace some of the

tissue surrounding the finding thus obscuring the view. This allows a better definition of detail and thus a better image of the lesion[20].

As defined by Morrow and colleagues and adapted by the American College of Radiology the following classification is used to define the level of suspicion and further investigation recommended, on the basis of the diagnostic mammography[20,22]:

Category	Level of suspicion	Investigation recommended
1:	Benign; no suspicion of cancer.	None
2:	Low risk; probability of cancer <2%	CBE + mammogram at 6 and 12 months
3	Intermediate risk; probability of cancer 2%-10%	Image guided Fine Needle Aspiration (FNA) or core biopsy
4:	High risk; probability of cancer > 10%	Complete excision

Table 1: American College of Radiology classification of mammographic findings

According to the Canadian Clinical Practice Guidelines, patients with category 1 abnormalities do not require any further investigation and should be followed with routine screening (Figure 5B)[20]. Patients with Category 2 lesions should be followed-up with periodic clinical examination (Figure 5B). Follow-up examination of category 2 abnormalities should be carried out at approximately 6 and 12 months. If the abnormality is stable, examination should be repeated annually for 2 to 3 years thereafter.

Those with Category 3 mammographic findings, require only a sample of cells or tissue from the tumor obtained by incisional biopsy. If the tumor is not palpable, the biopsy should be guided by either ultrasonography or stereotaxis, to allow visual localization of the lesion. Category 3 widespread calcifications or lesions that cannot be localized in the stereotactic views should be undergo a surgical biopsy (Figure 5C) [20,23-27].

Category 4 abnormalities should be completely excised (excisional biopsy) (Figure 5C). If the lesion is not palpable it should be localized with the guidance of either ultrasonography or stereotactic imaging. Once localized, a wire is inserted as close to the lesion as possible and stabilized in place. During surgery, the surgeon localizes (finds) the lesion by following the wire into the breast. This combination of image guided localization and open excisional biopsy is referred to as "wire localization excisional biopsy" and is the conventional surgical technique used today for the excision of non-palpable mammographic abnormalities.

When surgical biopsy is carried out for category 4 abnormalities the lesion must be completely removed with no remnants of tumor (residual tumor) neither in the breast nor in the surrounding margins of the excised specimen. The intact pathology specimen should be examined radiographically to confirm that all abnormalities observed in the mammogram have been removed[29-36].

In addition to Category 4 mammographic lesions, other indications for wire localization excisional biopsy are: a) disagreement between the assessment of the mamographic finding and the results of the incisional biopsy; b) noticeable change in the mammographic findings over time; c) the incisional biopsy demonstrates atypical hyperplasia. This is associated with over 50% risk of multiple malignancies coexisting, known as multicentricity[14,15].

The following factors may be obstacles in the success of conservative surgery for breast cancer treatment[39-68, 72,77,78,80]. Larger tumors are more difficult to remove with enough surrounding healthy breast tissue without removing a large portion of the breast[91-99]. The presence of an intraductal component is often associated with widely spread malignant microcalcifications through a very large area of the breast. Because they are so widespread, it is very difficult to achieve complete excision of these microcalcifications with conservative surgery[91-99,104]. Surgical scars and cicatricial tissue in the breast do not allow the lesion to be visualized clearly. Consequently, it cannot be localized accurately and excised adequately[102-104]. The younger the patient the higher the density of the breast tissue. The accuracy of detection of mammographic findings decreases as breast density increases[104].

1.1.5 WIRE LOCALIZATION EXCISIONAL BIOPSY

The following sections describe the wire localization technique, its advantages, and limitations.

Non-palpable breast tumors present a challenge because these tumors cannot be localized with physical examination. Therefore, preoperative mammogram followed by wire localization is required for the surgeon to find the lesion and perform the biopsy. Before surgery, the lesion is localized under mammographic, ultrasonographic, or stereotactic guidance and a wire is inserted as close to the lesion as possible and stabilized in place to prevent the wire from moving away from the lesion. This wire acts as a guide for the surgeon to find the lesion in the breast or the area of the breast with the lesion and to excise it.

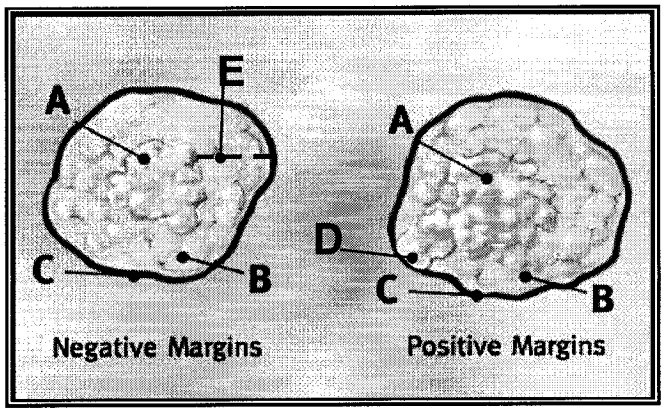
The size of breast tissue removed by wire localization excisional biopsy is affected by two opposing requirements. On the one hand the surgeon aims to achieve adequate local control of the disease by removing the tumor within wide enough healthy breast tissue and microscopically clear margins while on the other hand trying to remove the least possible breast tissue in order to avoid disfiguring of the breast. The main determining factors of the amount of tissue removed are the proximity of the tip of the wire to the target lesion and the size of the lesion to be excised[36,37]. The success rates reported in the literature

in placing the tip of the wire-guide within 10 mm from the lesion is between 80% and 96%[36-41].

In centers where this approach has been employed as a definitive therapeutic procedure to remove the tumor, 40-59% of patients require further supplementary surgery after the biopsy[36,46,47]. Based on these results, the therapeutic role of wire-guided biopsy remains controversial[47,48].

1.1.6 MARGINS, RESIDUAL DISEASE AND LOCAL RECURRENCE

Current advances in surgical assessment and treatment of breast cancer are aimed at maximizing conservation of breast tissue. The most important parameter that indicates whether or not a tumor has been completely excised, with conservative surgery, is the clarity of the surgical margins. Surgical margin refers to the width of healthy breast tissue surrounding the tumor within the excised specimen. It is measured as the shortest distance between the outer edge of the tumor and the external border of the excised specimen (E) as shown schematically in figure 7 below.



A = malignant tumor
B = healthy breast tissue
C =external border of excised specimen
D =involved margin
E =clear margin

Figure 7: Schematic of specimen with negative (clear) margins and positive (involved) margins.

The term "clear margins" means that the tumor has been removed with enough healthy tissue around it to consider that the excision is complete and the entire tumor has been removed (Figure 7). Contrary, the term "involved margins" means that the tumor touches the external border of the excised specimen or that the healthy breast tissue surrounding the tumor is not wide enough for the excision to be accepted as complete (Figure 7). In other words, when a tumor is excised within involved margins there is reason to believe that part of the tumor has remained in the breast after the biopsy.

Data in the literature show that approximately 50% of excisional biopsies, with a range between 20% and 70%, have involved margins and residual malignancy in the surgical margin or within 1mm from the outer border of the excised specimen [49-52]. It has been shown that surgical margins of tumorectomies that are infiltrated by malignant cells or equivocal (either because of a faulty specimen or because of lesion

fragmentation) are associated with approximately 48% (ranging from 29-65%) probability of residual disease in the breast at the area of the excised tumor[47,53-58].

The tendency of breast cancer to spread subclinically into the surrounding breast parenchyma make it difficult to assess histological margins[50,51]. This may explain why 30% of those biopsy excisions with clear margins subsequently had residual tumor upon re-excision while 48% of patients diagnosed with involved margins had no residual tumor[41].

The most common reason for a false-negative assessment of surgical margins is an incomplete examination of the outer surface of the specimen. To prepare a specimen 2 cm in diameter for histological analysis, it is sliced by the microtome to approximately 3,000 sections which are dyed and processed on slides for microscopic assessment. The larger the specimen the higher the number of slides prepared. Therefore, in order to analyse a complete 2cm specimen, the pathologist needs to examine more than 3,000 slides. Due to limitations in time and budget, this is unfeasible so pathologists resort to a random examination of as many sections as possible[50]. As a result, the assessment is incomplete. Since the diagnostic accuracy of the surgical margins is directly related to the number of sections assessed an incomplete assessment has an increased probability of a false negative analysis of clear margins[50].

The controversy on the width of surrounding healthy tissue required for the surgical margins to be considered as "clear" is still ongoing and differs depending on the type of tumor. For invasive ductal carcinomas the minimum margin width considered as safe varies between 1mm and 2 mm[40-47,53-90]. Intraductal carcinomas otherwise referred to as non-invasive or carcinoma in-situ, are the least aggressive cancers that are usually widespread but rarely metastasize outside of the breast. However, due to the multifocality of intraductal carcinomas, the controversy is more complicated. Until recently, a clear margin was considered as that with a width of at least 1mm[53-68,91-99,151]. In 1999, Silverstein retrospectively evaluated the impact of radiotherapy in relation to the width of surgical margins on 469 patients, treated at the Van Nuys Breast Center, who had been submitted to breast conservation surgery for intraductal carcinoma. The results of this study indicated that postoperative radiation therapy did not reduce the risk of local recurrence for patients with surgical margins of 10mm or more. However, for patients with margins less than 1mm wide, radiotherapy significantly reduced the risk for local recurrence. For the patients with margins greater than 1mm and less than 10mm, the risk was not significantly reduced by submitting the patients to postoperative radiation therapy [53]. In 2003, further evaluation of the same patients as well as additional patients with DCIS treated at the Van Nuys Breast Center and at the USC/Norris Comprehensive Cancer Center produced similar results as in

1999 for margins 10mm or greater and less than 1mm[54]. Contrary, the results changed for patients with intermediate margins (1mm to less than 10mm) showing a statistically significant decrease of risk for local recurrence after postoperative radiotherapy[54].

Due to the strong association between the clarity of reported surgical margins with the incidence of local recurrence rate over 3 to 5 years postoperatively, it is considered mandatory to assess the margins of the excised tumor and breast tissue (specimen) immediately after excision[69-80]. This is done by cutting a piece of the specimen, deep freezing it and marking the edges with a specific dye (referred to as frozen sections). However, the usefulness of frozen sections has been limited by the relatively high proportion of false negatives[81,84]. The use of frozen sections has been discouraged for small (<10mm) and nonpalpable breast lesions because of the fear that manipulation of the specimen may render the tumor undetectable or permanent sections from the frozen piece (frozen block) may be suboptimal or even useless for definitive diagnosis[70,83,84]. Thus, no optimal method for assessing the microscopic margins of a breast tumor specimen has been established.

1.1.6.1 Post-biopsy residual malignancy

Residual malignancy is defined as remnants of malignancy in the area of the breast from where a malignant tumor has been removed. The presence of residual malignancy after breast conserving therapy is

responsible for the majority of early recurrences close to the primary site[39-41,53,54,72-99].

As mentioned above, the size of the tumor, intraductal carcinoma, scar tissue and breast density present a challenge for the success of conservative breast surgery. In addition, the presence of residual microcalcifications on post-biopsy mammograms, the pathologic status of axillary lymph nodes and preoperative chemotherapy have also been shown to be directly associated with the risk of residual malignancy[40,42,58,68,70,100-108].

Evidence has shown a strong association between tumor pathology and residual cancer. The probability that a tumor will be excised with involved margins is 82% for patients with intraductal carcinoma, 75% for those with invasive lobular carcinoma (highly multifocal) and 50% for patients with invasive ductal carcinoma (one lesion)[39-41,52,53,76-78,91-103,151].

1.1.7 RATIONALE FOR THE NEED OF ALTERNATIVE SURGERY OPTIONS

Wire localization excisional biopsy is currently the surgical technique of choice for non-palpable breast lesions detected only with mammography. The advantages of wire localization excisional biopsy are primarily the excision of an adequate specimen for an accurate

histopathological diagnosis, the minimal post-operative complications, the removal of less breast tissue than partial mastectomy, and the shorter hospitalization of the patient[41-44].

However, wire localization excisional biopsy has certain disadvantages. First, it is a multiple step process. The patient begins the process in radiology, where the wire-guide is inserted in the breast under mammographic guidance. The patient is then taken to the operating room for the biopsy, which may be done under local or general anaesthesia, depending on the preference of the surgeon[105]. The lesion is then localized, and the specimen is excised containing the wire guide and the part of breast tissue surrounding it.

The excised specimen is taken to radiology where it is X-rayed and evaluated for the following three criteria; a) to determine if the specimen contains the target lesion, b) if the whole lesion is excised and c) if the margins of the specimen are clear. If all three criteria are satisfied the biopsy is considered complete. If one or more of the above criteria is not satisfied the surgeon excises more breast tissue around the borders of the surgical cavity (opening) and removes a second specimen which is also send to radiology. The process is repeated until the complete excision with all the specimens included satisfies the three criteria listed above (a-c). This results in a longer duration of surgery, and anaesthesia, especially if general anaesthesia is used, and multiple fragmented specimens which make the final pathological assessment of

margin clarity very difficult[27-34,81,84,100-124]. Evidence shows that in as much as 20-25% of the cases the lesion is not found in the initial specimen and that the macroscopic margins are involved in 59.4%, ranging from 47% to 92%[35-40,52-99,116-124].

Considering the importance of radiologic imaging for the success of wire localization excisional biopsy it is important to note that the accuracy of imaging in predicting the status of the specimen's margins or the presence of residual tumor has been shown to be limited[31-40]. In 40-59% of the cases, specimens considered to have clear margins by imaging, were shown to have involved margins after the specimen was examined by pathology[23,31-40]. This is important because the reported rates of residual cancer at re-excision after positive surgical margins vary significantly between studies from 22-64%[23,32,36,86,116-124].

Given these problems with localization and excision accuracy with wire localization excisional biopsy, more accurate techniques that would improve the intraoperative localization of the tumor and the verification of its removal within the excised specimen have been sought. In the late 1990s, the ABBI, a breast biopsy system was developed which combines stereotactic imaging (3-dimensional localization of the lesion under digital mammography guidance) along with a large 2cm coring device used to excise the tumor.

1.2 ABBI EQUIPMENT DESCRIPTION

The Advanced Breast Biopsy Instrumentation (ABBI) system involves the stereotactic localization and the excision of a core shaped breast tissue specimen 20cm in diameter in one step, under local anaesthesia. A surgeon performs the ABBI procedure with the assistance of a radiology technician in the day-surgery outpatient clinic, whereas wire localization excisional biopsy, is done in the operating room and requires hospitalization of the patient.

The ABBI has four parts. First, there is a custom designed table for the patient to lie on. The second part is a computer, equipped with customized software for stereotactic localization. The computer is connected to the table which has a built-in digital mammogram x-ray machine (the third part) and then all of this is connected to a small surgical coring device (the fourth component), which actually performs the biopsy. The detailed description of the ABBI components is in Appendix 5.

2 REVIEW OF THE LITERATURE

A search of the medical literature for publications on the evaluation of the ABBI identified 313 studies of which 282 were excluded. Of these, 179 were excluded because they were individual case reports, studies with less than 10 patients enrolled or not focusing on the ABBI system in the management of non-palpable mammographic findings. Another 77 were narrative reviews, 21 were expert opinions, and 5 were repeated publications. There were 26 remaining clinical studies used in the literature review. These are discussed in the following section and are listed in appendix 6A[125-150].

2.1 SAFETY

Adverse events were reported in only 14 of the 26 reviewed studies[125,126,128,131,134-137,139,140,142,144,148-150]. The overall incidence of the adverse events reported in these 14 studies is low (2.5%) and not clinically significant. On the other hand, there was no predefined categorization of adverse events, hence, the definition of adverse events between the studies varied. Given the above, a detailed quantification of the adverse events reported in the literature and a credible synthesis of the safety data of the ABBI procedure is difficult.

A total of 165 (5.6%) adverse events and complications were reported among the 2949 total patients enrolled in all 14 studies reporting adverse events (Appendix 6B,6C). Among these, technical

failure or mechanical malfunction was reported in 81 cases (2.8%)[126,130,136,139,146]. Technical problems included poor calibration, cautery / snare failure, T-bar failure, computer malfunction, lesion displacement. The most frequent treatment related adverse event in the reviewed studies was haematomas, reported in 47 cases or 1.6% of the total ABBIs performed[125,126,128,130,133-136,138,139,141]. Followed by vasovagal reactions [130,133,139] and wound infections, reported in 8 and 7 cases respectively[133,135,139,141].

2.2 EFFECTIVENESS

2.2.1 MICROSCOPIC SURGICAL MARGINS CLEAR OF MALIGNANCY

A total of 940 ABBI biopsies were performed in the 16 studies that reported the margin status of the excised specimens [125,126,136,138,141,143,145,148-150]. Of these, 328 (35%) tumors were excised within clear healthy margins (Appendix 6D). The proportion of involved microscopic margins was 65% ranging from 57-95% of the malignant tumors. Amongst the 940 biopsies performed, 210 (22%) tumors were diagnosed as malignant.

2.2.2 DURATION OF PROCEDURE

There were 20 studies that reported duration of procedure[126,128-141,143,145-149]. The mean duration of the ABBI was approximately 35 minutes, varying from 20 to 80 minutes. In the majority if these studies it

was not clear whether the time taken to complete the procedure included only the time required for the actual excision of the specimen or the preparatory stage as well, including the time required for initial localization of the lesion, haemostasis, suturing and wound dressing.

2.2.3 UNSUCCESSFUL EXCISION

Two authors Smathers and Bloomston reported 2 cases in 100 (2%) and 1 of 55 (1.8%) respectively of unsuccessful excisions where the lesion was not found in the excised specimen but remained in the breast[126,145].

2.2.4 SUPPLEMENTARY SURGERY REQUIRED

The type of supplementary surgery required after an ABBI procedure is either a lumpectomy or a modified radical mastectomy. Of the 663 patients enrolled in the 8 studies reporting supplemental surgery, 117 (18%) were submitted to either lumpectomy or modified radical mastectomy. The frequency of subsequent surgery ranged from 8% to 42%, with lumpectomy being the supplementary surgery in most cases (Appendix 6E)[125,126,128,131,136,138,139,141].

2.3 PERFORMANCE VOLUME ASSOCIATION

None of the studies explored a possible association between the effectiveness of the ABBI and the characteristics of the surgeon.

2.4 PATIENT SATISFACTION

Four of the 26 studies reported patient satisfaction[125,134,135,139]. The assessment tools and outcomes varied. La Raja et al interviewed patients by telephone 24 to 48 hours after the ABBI and reported excellent satisfaction in general without any specific data[135]. Perelman et al reported local pain and discomfort during the procedure in 4 (12%) of the patients[139]. Atallah et al reported in general that women tolerated the procedure well[125]. Kelley et al reported only on prescription analgesics used post-operatively[134]. They stated that 2.4% of their patients used prescribed pain medication. Overall, all 4 authors reported that patients were satisfied with the ABBI but detailed information has not been presented.

2.5 ECONOMIC EVALUATION

None of the published studies included a cost-effectiveness evaluation of the ABBI. Matthews et al reported an average hospital patient charge for an ABBI of $2,377 versus $3,028 for wire localization excisional biopsy ($P < 0.05$), an average saving of $650 per patient[138]. LaRaja et al reported an average savings with the ABBI as compared to wire localization excisional biopsy of $1,000 per patient[135]. Most of the savings are shown to be the result of the ABBI procedure being performed as an outpatient procedure with the use of local anaesthesia, thereby eliminating the fee for preoperative testing, anaesthesia,

operating room, and recovery room. Most studies reported direct costs of the ABBI compared with other procedures without taking into consideration the cost of the patient's complete surgical management including supplementary surgery.

2.6 COMPARATIVE STUDIES

Among the 26 studies reviewed 3 presented a comparison between the ABBI and wire localization excisional biopsy. One study reported only clinical results, two compared clinical results and patient satisfaction and one reported only patient satisfaction (Appendix 6F-6G)[127,129,146]. D'Angelo et al compared 23 patients treated with an ABBI and 23 patients operated by wire localization excisional biopsy[129]. Equal numbers of breast cancers were excised by both techniques, all of which were excised with involved margins. Even though the quantity of blood loss reported was less for the ABBI the statistical significance of this difference was not reported. Detection of residual cancer was reported in more ABBI cases than in wire localization excisional biopsies but again the statistical significance of this difference is not mentioned[127,129,146].

Velanowich compared 104 ABBIs to 520 wire localization excisional biopsys and 245 core needle biopsies[146]. Technically successful biopsy was defined as a case for which the radiologist or surgeon performing the procedure was satisfied that enough tissue had

been removed to produce a pathologic diagnosis. There was no significant difference between the three techniques in technical success rate. Significantly more malignant tumors were excised with wire localization excisional biopsy (35%) versus ABBI (14%) and core needle biopsy (20%) ($p<0.01$). The effectiveness of the ABBI to excise the breast lesion was 100% while the effectiveness of the core needle biopsy was (87.5%). Respective values for wire localization excisional biopsy were not reported. The subgroup of patients, for which repeat biopsy was required, included cases of technical failure occurring and conflicting mammographic / pathologic interpretations. The authors report that all the ABBI reexcisions resulted from technical failure in the first 30 cases. No technical failure occurred in the remaining 74 cases. Technical failure accounted for 25 of the reexcisions in the patients undergoing wire localization excisional biopsy[146].

In patients with malignant lesions, 63.6% of ABBI biopsies had positive margins, of which 71.4% had residual carcinoma on reexcision or mastectomy. In comparison, of the malignant lesions diagnosed with wire localization excisional biopsy, 50.9% had positive margins, of these 70.4% had residual carcinoma in the definitive lumpectomy or mastectomy specimen. Even though the statistical significance level of this difference is not reported, it is mentioned to be not statistically significant (Appendix 6F). With regards to safety, the author reported 30 cases of technical failure with the ABBI, all of which occurred in the first 30

cases, but did not report any safety data on the wire localization excisional biopsy cases. D'Angelo reported no complications in any of the 23 cases evaluated[129].

D'Angelo et al reported that patient acceptance of the ABBI was high, with 21 (91.3%) of the 23 patients evaluated reporting subjective assessment of comfort as excellent, 2 as good and 1 as poor. For patients operated by wire localization excisional biopsy, patient satisfaction has been reported in general as high, without any further information. For the ABBI, cosmetic results were 'excellent', according to a subjective assessment by both the patient and the surgeon. In comparison, cosmetic results after wire localization excisional biopsy were rated as acceptable by both the patient and the surgeon[129] (Appendix 6G)[129].

Chun performed a retrospective telephone interview, two years post-operatively, comparing the cosmetic results and satisfaction of 20 patients treated with the ABBI and 20 treated with wire-localization[127]. In this study 95% of ABBI patients reported excellent satisfaction with the cosmetic results of the technique and 75% reported excellent overall satisfaction; 25% were dissatisfied. Among the wire localization excisional biopsy patients, 25% reported excellent cosmetic satisfaction and 55% evaluated the results as acceptable cosmetically. However, more (90%) wire localization excisional biopsy patients reported excellent overall satisfaction with the technique as compared to 75% for

the ABBI. The statistical significance of these differences was not reported. The Velanovich study did not report patient satisfaction or cosmetic results[127].

2.7 CONCLUSIONS OF THE LITERATURE REVIEW

A total of 26 studies were reviewed of which 15 were observational non-randomized trials[125,126,128-130,133-137,139,141-143,148-150] and the remaining 9 were retrospective reviews of patient charts[127,131,132,138,140,144-147].

The most frequently reported adverse event was haematoma, with a frequency of 1.6%, vasovagal reactions (0.3%) and wound infections (0.2%). The adverse events associated with the ABBI were more often the result of equipment failure.

In order to evaluate effectiveness, researchers have compared the ABBI with wire localization excisional biopsy and core needle biopsy. When comparing the ABBI with core needle biopsy, diagnostic effectiveness was similar. On the other hand, technical problems are more frequent with the ABBI versus core needle biopsies.

Compared to wire localization excisional biopsy, duration of procedure and mean blood loss were lower for the ABBI. The frequency of reported supplementary surgery is lower among the ABBI cases than

wire localization excisional biopsy. No significant differences were found between the two techniques for clarity of surgical margin.

Patient satisfaction with the ABBI was generally reported to be from good to excellent. In conclusion, the results from these studies have suggested that the ABBI may cost less than wire localization excisional biopsy but be associated with higher risk of surgical complications. Similar successful excisions of tumors with clear margins have been reported for the ABBI and wire localization excisional biopsy. Therefore, more studies are needed to determine whether the ABBI should be used as a diagnostic and therapeutic procedure for breast cancer. The performance volume association for the ABBI has not been evaluated. This is important for the decision to implement the ABBI. Economic evaluation has been conducted for the ABBI but not within the Canadian Healthcare System. The current study addresses these needs.

3 PURPOSE, MATERIALS AND METHODS

3.1 RATIONALE AND PURPOSE

3.1.1 RATIONALE

For any new surgical technique to be implemented in routine clinical practice it must be proven to be superior to or more cost effective than other techniques indicated for the management of the same condition. Ideally, the technique under investigation should combine both clinical superiority and higher cost effectiveness over the traditional technology used.

Mammographically guided wire localization combined with open excisional biopsy has been the standard evaluation of non-palpable mammographic lesions. The investigation and management of non-palpable mammographic findings requires the complete surgical excision of the lesion within safe surgical margins (at least 1 mm of peripheral healthy tissue). Traditionally, this is performed by mammographically guided wire-localization combined with open excisional biopsy under either local or general anaesthesia. The probability of invaded margins after a wire localization excisional biopsy ranges from 29.5% to 79% with a mean of 59.4% [36-40,55,65-67]. Depending on the protocol followed at the institution where the surgery is performed and the experience of both the surgeon and the radiologist involved in the procedure, 40-59% of patients require post-biopsy supplementary surgery[27, 28,34].

The type of anaesthesia used during the excisional biopsy of the wire-localized lesion is either general or local. Data in the literature suggest that the type of anaesthesia does not affect the accuracy of tumor localization but local anaesthesia has a negative impact on the ability of the surgeon to achieve clear surgical margins[27-34,81,84,100-124]. This is more prominent for lesions located deeper that 3cm in the breast, for lesions located by a needle travelling for longer than 3 cm in the breast, or for microcalcifications because they are more difficult to localize[86]. On the average, 66% of all wire guided open excisional biopsies in North America are performed with general anesthesia[86].

It is estimated that 40-59% of all patients submitted to wire localization excisional biopsy will require a supplemental partial mastectomy and approximately 26-40% of these are operated under general anaesthesia[27-34,81,84,100-124]. Therefore, the probability that a patient who underwent wire localization excisional biopsy excisional biopsy will be submitted to general anaesthesia twice within a very short time period of 2-4 weeks is 10-24%.

A significant disadvantage of wire localization excisional biopsy is that it involves a three-step process. First, the patient must be taken to radiology for the lesion to be localized and the wire inserted, second, to the operating room for the biopsy and third, to the recovery room, where the patient will remain until discharge which may be from 24-72 hours after surgery.

The ABBI combines stereotactic imaging (3-dimensional localization of the lesion under digital mammography guidance) along with a 2cm. coring device. The ABBI allows the stereotactic localization and the excision of the whole tumor in one step, under local anaesthesia and in the day-surgery outpatient clinic.

Given the limitations of the currently used methods, a new technique that may be more effective, safe, and cost-effective would be useful. The ABBI has been developed to address this need. The current study evaluated the ABBI as a diagnostic and therapeutic intervention for the management of breast disease.

3.1.2 STUDY OBJECTIVES

The objectives of the study are:

1. To evaluate the diagnostic effectiveness of the ABBI system for the management of breast disease;
2. To evaluate the therapeutic effectiveness of the ABBI system for the surgical management of breast cancer;
3. To evaluate the safety of the ABBI system as a surgical technique for the management of breast lesions;
4. To describe patient satisfaction with the ABBI;
5. To evaluate the volume performance of the ABBI;

6. To describe the cost evaluation of the ABBI.

3.2 STUDY DESIGN

The study was initiated in the Montreal General Hospital in September 1997 and enrolled patients both retrospectively and prospectively. The data of patients that underwent an ABBI between October 1995 and September 1997 were abstracted retrospectively from patient charts in the Montreal General Hospital Archives and the Montreal General Hospital Breast Clinic. From September 1997 until December 2001 patients operated on with the ABBI were enrolled prospectively. Between September 1997 and July 1999 the patients enrolled in the study were operated only in the Montreal General Hospital and from July 1999 to December 2001 patients were also recruited and operated at the Sacré Cœur Hospital of Montreal.

3.2.1 PATIENTS:

All women referred to the Breast Clinics of the Montreal General Hospital, the Sacré Cœur Hospital of Montreal or St. Mary's Hospital for further evaluation of a non-palpable mammographic finding were eligible to participate in the study.

3.2.1.1 Recruitment Procedures:

Doctors from these three breast clinics recruited patients and referred them to the Montreal General Hospital or the Sacré Coeur Hospital of Montreal where the ABBI was performed by one of three surgeons that performed the ABBI. The first and second surgeons operated on all their patients in the Montreal General Hospital and the third operated in the Montreal General Hospital from September 1997 to July 1999 and the Sacré Coeur Hospital from July 1999 to December 2001.

All potentially eligible patients underwent physical examination and their mammograms were reviewed by the treating or referring surgeon. Those with non-palpable mammographic findings requiring further surgical investigation were given the choice, by the treating surgeon, between two different surgical techniques, the wire localization excisional biopsy or the ABBI. The surgeon described both techniques to the patient and explained the advantages and disadvantages of each. Patients selected the technique on their own. Patients selecting the ABBI were included in the study.

3.2.1.2 Inclusion Criteria:

Patients who chose the ABBI and fulfilled all of the following inclusion criteria were enrolled in the study:

1. Non-palpable mammographic finding with a maximum diameter less than 2cm.
2. Mammographic finding of a lesion requiring excisional biopsy and appropriate for the ABBI.
3. Distance of at least 15 mm between the tumor and the chest wall.
4. Able to lie prone for the duration of the procedure.
5. No medical history of severe cardiac or pulmonary disease.
6. Not pregnant.
7. Understand and sign an informed consent form agreeing to undergo the procedure.

3.2.1.2.1 Explanation of Inclusion Criteria

1. Non-palpable mammographic finding with a maximum diameter less than 2 cm.

The size of the tumor was recorded as the length of the longest diameter. According to clinical guidelines, tumors eligible for an excisional biopsy with the ABBI system should not be larger than 2cm in diameter, as measured by digital mammography. This restriction is placed because of two reasons:

a. Lesions larger than 2cm in diameter are usually large enough to palpate so there is no need for image-guided localization; therefore, the lesion does not qualify for an ABBI.

b. At the time of the study the larger coring device available for the ABBI had a diameter of 2cm. Any tumor larger than 2 cm would exceed the coring device and would not be excised completely.

There is one exception to this rule. Microcalcifications that were widespread through the breast, consuming an area larger than 2 cm. In this case, the ABBI was performed solely for diagnostic purposes.

The distinguishing feature of the shape and distribution of microcalcifications that would raise a suspicion of a possible malignancy is that of dense groups together or clusters. Any specific area in the affected breast where the calcifications are more densely grouped together or actually form clusters was chosen as the most representative of the pathology of the lesion and was thus chosen as the target to be excised by the ABBI.

Types of mammographic findings eligible for an ABBI biopsy are, i) a soft tissue nodule or mass, defined as any group of cells clustered together more densely than the surrounding tissue; ii) microcalcifications, characterized by minute calcium deposits (<0.5 mm in diameter) in the breast and iii) a combination of both soft tissue nodule and microcalcifications. Microcalcifications are indications of early breast cancer. In 95% of all DCIS and 75% of occult cancer they occur alone, as the only mammographic abnormality[91-99].

2. Distance of at least 15mm between the tumor and the chest wall

One of the most important criteria for eligibility for an ABBI biopsy, is the thickness (width) of the breast under tight compression. This is directly proportional to the size of the breast. Figure 8 is a graphic description of the breast compressed between the two ABBI compression plates which are the X-Ray receptor and the surgical window panel.

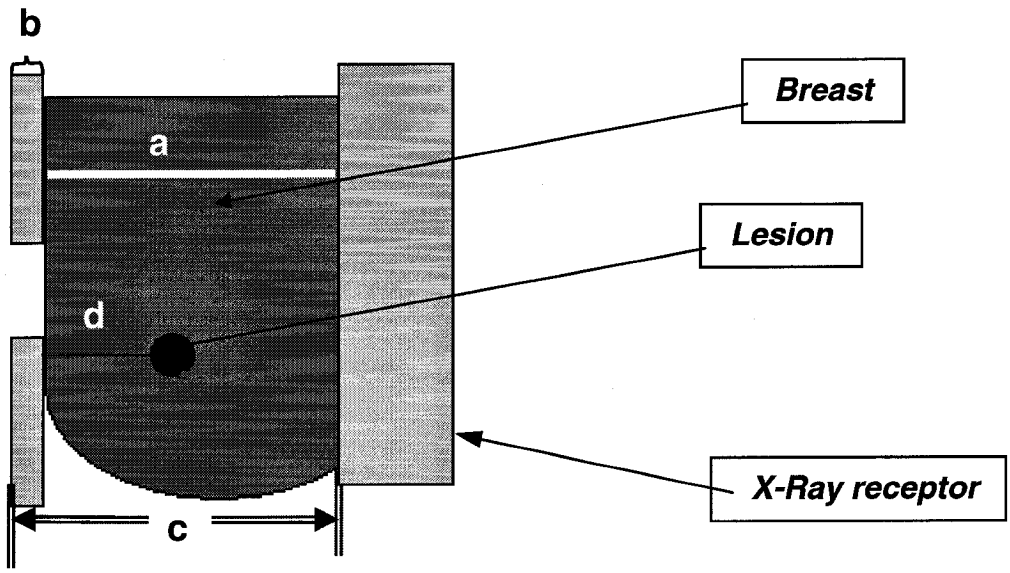


FIGURE 8: Graphic description of breast compression
b = 12mm thick, c = a + b

Eligible if: **c - d ≥ 15mm** or if **p + b ≥ 15mm**

Where:

- a = breast thickness
- b = surgical panel thickness
- c = breast compression as measured
- d = depth of the target lesion
- p = posterior margin or distance between the target and the opposite side of the breast which corresponds, in this case, to the X-Ray receptor inner surface.

Breast compression is measured as the distance between the outer surface of the surgical window panel (b) and the X-Ray receptor. As shown in figure 8, the thickness of the surgical panel, is 12 mm. Hence, the actual thickness of the breast (a) is the breast compression (c) - 12mm. In order to ensure an adequate excision with a safe posterior margin, so that the surgical cannula will not cross through to the opposite side of the breast, the thickness of the breast under compression should exceed the depth of the target by at least 15 mm or the posterior margin (p) plus the surgical window panel totals at least 15mm.

3. The patient should be able to lie prone for the duration of the procedure

The average duration is estimated to be between 50 and 60 minutes for less experienced surgeons and approximately 15-30 minutes for more experienced surgeons. The patient should be able to lie prone for the appropriate amount of time. It is obligatory to remain motionless throughout the procedure so as to prevent the target from moving. This makes it even more difficult for patients with cardiac or pulmonary disease. The slightest movement of the breast could result in spontaneous movement of the target and thus the initial dimensions measured would be non-applicable and the localization would need to be repeated.

4. No medical history of severe cardiac or pulmonary disease

A patient suffering from severe cardiac or pulmonary disease may not be able to remain in the prone position for the duration of the procedure.

5. The patient should not be pregnant

The ABBI operating table is not designed for pregnant patients. This makes it difficult for pregnant women to lie prone on the table, for the duration of the procedure.

6. The patient should understand and sign an informed consent form agreeing to undergo the procedure.

A bilingual informed consent form was given to the patient prior to surgery and after the description of the procedure and demonstration of the equipment. For ethical reasons, it was obligatory for the patients to understand and sign the consent form in order to be enrolled in the study Appendix 7.

3.2.1.3 Exclusion Criteria:

Patients with one or more of the following criteria were not eligible to participate in the study:

1. The lesion could not be visualized by digital mammography
2. Palpable lesion with a diameter greater than 2 cm.

3. Inability of the patient to understand the description of the technique and sign the operative consent form.

3.2.1.3.1 Explanation of Exclusion Criteria

1 Inability to visualize the lesion with digital mammography

If the lesion detected in the breast is either at the extreme superior part of the upper quadrant or extreme posterior part of the breast near the chest wall, it cannot be positioned within the boundaries of the 10 X 10 cm operating window for the image to be taken. This makes it impossible for the lesion to be visualized by the digital mammography.

2 Palpable lesion or lesion with a diameter greater than 2 cm

Lesions that are 2 centimetres or more in diameter are usually palpable and can be detected by self-examination or a physical examination. A palpable tumor of this size is manually localized and easily removed without the need for guidance by imaging technology.

3 Incapacity of the patient to comprehend the description of the technique and sign the operative consent form

Every effort was made to communicate to the patient the advantages and disadvantages of the ABBI and to describe and demonstrate the technique and the equipment to the patients or the accompanying person if the patient was not capable of understanding or

communicating in English or French. If the patient still could not communicate, the procedure could not take place for two reasons. The equipment used and the environment the ABBI is performed in are not the traditional operating room that the patient may recognize. This will create an additional discomfort and anxiety for the patient. This discomfort will be increased by the fact that the procedure is performed under local anaesthesia and requires the patient to remain motionless and to express only verbally the occurrence of discomfort or pain. The inability of the patient to communicate her feelings will normally result in nervous movement. Any movement of the patient may easily move the breast and the target lesion from the precalculated coordinates. This will result either in missing the lesion during the excision or to the necessity to repeat the entire procedure. Furthermore, complete understanding of the procedure and the study are essential for informed consent. These patients were excluded for practical and ethical reasons.

3.3 DATA SOURCES, STORING AND ANALYSIS:

Data were abstracted and entered by the candidate (Fotini Sampalis) and stored in Excel™ spreadsheets. Data analysis was performed with SPSS 11.0 for Windows. From October 1995 until September 1997 data were abstracted from patient charts retrospectively. Charts were reviewed either at the Montreal General Hospital Archives or the Montreal General Hospital Breast Clinic. From

September 1997 until July 1999 at the Montreal General Hospital and from July 1999 to December 2001 at the Sacré Coeur Hospital, patient demographics were recorded immediately prior to surgery and surgical data were recorded directly after the procedure. Information on histological analysis, adjuvant therapy recommendations, details on adjuvant therapy performed and patient follow-up was abstracted from the patient charts in the respective clinics. Between July 1999 and December 2001 data of patients operated at the Montreal General Hospital were abstracted from patient charts at the Montreal General Hospital Archives or the Montreal General Hospital Breast Clinic.

3.4 THE VARIABLES OF THE STUDY

The variables used in this study and the source of the data are described in the following section. These variables are described in the study "Case Report Form" included in Appendix 8.

3.4.1 PATIENT'S CHART:

The data abstracted from the patient's chart were the patient demographic information, past medical history, mammographic report results, histology report results, information on supplementary surgical treatment, adjuvant therapy suggested by the oncology board and follow-

up for the duration of the study. In detail, the specific variables derived from the patient's chart were:

1. Basic Demographics:
    a. Medical record number
    b. Date of birth
    c. Ethnic background
2. Medical History Unrelated To Breast:
3. Medical History Related To Breast:
4. Mammographic Report
    a. Date of last mammogram
    b. Level of suspicion for the lesion detected as reported by the radiologist
    c. Indication for procedure: (type of mammographic finding)
    d. Quadrant: where the lesion was located
    e. Mammographic size of lesion
5. Histologic Report:
    a. Tumor pathology classified as benign or malignant. Benign tumors included fibroadenomas, cysts, sclerosing adenosis, fibrocystic breasts, and atypic hyperplasia. Malignant tumors included infiltrating ductal carcinoma, ductal carcinoma in situ

(DCIS), mixed infiltrating ductal carcinoma and DCIS, infiltrating lobular carcinoma, lobular carcinoma in situ (LCIS) and mixed infiltrating ductal carcinoma and LCIS.

b. Evaluation of the microscopic margins of the excised lesion in order to microscopically (with the use of histologic preparation and microscopic inspection) confirm that the lesion has been excised within safe margins, meaning that it is surrounded by at least 1 mm of healthy breast tissue.

6. Supplementary surgical treatment required, as advised by the oncology board. This is mainly partial mastectomy with axillary lymph node dissection.

7. Follow-up for cosmetic results, complications, or recurrences through-out the 5 years of the study.

3.4.2 SURGICAL REPORT:

The details of the ABBI procedure including the duration of the procedure, description of the lesion and surgical complications were abstracted from the "Surgical Report". The detailed variables derived from the Surgical Report were:

1. Date of the ABBI
2. Digital size of the lesion as seen in digital mammography
3. ABBI approach of excision (the side of the breast from which the

distance from the skin to the target is the shortest.

4. Breast compression (the thickness of the breast in mm after it has been compressed between the operating window and the image receptor) (Figure 8).

5. Depth of the lesion (Z-axis) (the perpendicular distance between the skin and the target, with the breast under compression) (Figure 8).

6. Posterior margin; the distance between the target and the opposite side of the breast which corresponds, in this case, to the X-Ray receptor inner surface (Figure 8).

7. Blood loss (in cc) estimated from the number of gauzes used during surgery.

8. Duration of the procedure in minutes; the time from localization to excision of the lesion and removal of the ABBI cannula from the breast.

9. Results of the evaluation of the post-biopsy digital mammogram for the presence of tumor remaining in the breast. This allowed the surgeon and the radiologist to assess whether the tumor was in the excised breast tissue (specimen) and if any parts of it are still remaining in the breast.

10. Results of the assessment of the digital image of the excised specimen for the identification of the target tumor in it. This

allows the surgeon and the radiologist to assess whether the tumor has been excised within the specimen as well as if it was excised completely.

11. Evaluation of the macroscopic (gross) margins of the excised lesion. The specimen is imaged and macroscopic margins are assessed with the naked eye. This is done to confirm that the lesion has been excised with enough healthy breast tissue around it, as can be seen by the naked eye.

12. If the assessment of the post-operative mammogram, the image of the specimen and/or the evaluation of the macroscopic margins indicated that the tumor was not excised completely, an immediate re-excision was performed. This was done either with a repeat ABBI or under direct vision like a conventional excisional biopsy. All reexcisions were reported.

3.5 PATIENT GROUPS ANALYSED:

Analyses was performed for the entire study sample as well as for subgroups of patients classified according to the following:

3.5.1 TYPE OF MAMMOGRAPHIC FINDING DETECTED:

Patients were divided in the following three subgroups according to the type of lesion detected by mammography:

a. Soft tissue nodule,

b. Microcalcifications

c. Combination of soft tissue nodule with microcalcifications.

3.5.2 LESION SIZE

The largest diameter of the lesion was recorder in millimetres.

3.5.3 QUADRANT OR LOCATION OF THE LESION

One of the important determinants of the ability of the surgeon to accurately localize and excise a tumor with the ABBI system is the location of the lesion. In order for the lesion to be localized and excised it must be placed in the center, or as close as possible to the center of the 10X10 cm operating window through which the surgery will be performed. Positioning the lesion near the edges of the operating window will not allow enough space for the coring device to pass through at a 90° angle to the breast. It is thus important that the efficacy of the ABBI is assessed not only for the total group of lesions but also within the subgroup of patients categorized by the quadrant of the breast the lesion is located in.

Women in this subgroup were divided in 5 categories depending on the quadrant of the breast the lesion was located:

a. Left or right breast:

i. lower outer

ii. lower inner

iii. upper outer

iv. upper inner

v. central

3.6 SPECIFIC METHODS TO ADDRESS STUDY OBJECTIVES

***OBJECTIVE 1:* To evaluate the diagnostic effectiveness of the ABBI for the surgical management of breast disease;**

The **diagnostic** effectiveness of the ABBI is measured by its ability to successfully localize and adequately excise the targeted lesion for histopathological diagnosis. This was determined by the radiologic assessment of the specimen. The radiologic image allows the radiologist and the surgeon to verify that the target lesion was removed completely.

The diagnostic effectiveness of the ABBI was defined as the proportion of excised specimens found to contain the target lesion among all specimens excised. This is calculated as the

$$\textit{Diagnostic Effectiveness (DE)} = \left(\frac{\textit{Number of excised specimens containing the target lesion}}{\textit{Total number of excised specimens}} \right) \textit{X100\%}$$

The analysis was based on malignant lesions only because therapeutic effectiveness is not relevant for benign lesions. Furthermore, once the lesion has been diagnosed as benign by the pathologist, no further treatment or reexcision is conducted, even if the margins are not clear. In many cases the pathologist may not report margin clarity for benign lesions.

OBJECTIVE 2: ***To evaluate the therapeutic effectiveness of the ABBI for the surgical management of breast cancer;***

The **therapeutic** effectiveness of the ABBI is measured by its ability to successfully excise the targeted malignant tumor within sufficient surrounding healthy breast tissue for clear surgical margins (>1mm), in order to avoid the need for supplementary excisional surgery. This was determined by the pathologist who examined the excised specimen.

The clarity of microscopic margins was determined by the histological examination of the specimen. Immediately upon excision, the margins of the specimen are labelled as upper, lower, lateral, or medial. The specimen was then sent to the pathology department where the margins were stained with a dye that adheres to tissue and is visible under the microscope. This procedure is simple and does not interfere with histologic evaluation. Its advantage is that it clearly distinguishes

surgical margins from margins formed by the cutting of the specimen with the microtome for histological evaluation. This is essential to assess if the excision of the tumor was complete (clear margins) or incomplete (involved margins).

The decision on whether supplementary surgical treatment is required depends on the clarity of all the microscopic margins around the excised tumor. If any of these margins is not clear, additional excisional surgery or partial mastectomy is required. The need for subsequent supplementary surgical excision of further breast tissue in order to achieve clear surgical margins is a direct measure of the effectiveness of the ABBI as a therapeutic surgical technique for malignant breast tumors.

Therapeutic effectiveness assessment was based only on the evaluation of the malignant lesions biopsied. This was defined as the proportion of malignant lesions excised with clear microscopic margins:

$$\textit{Therapeutic Effectiveness (TE)} = \left(\frac{\textit{Number of malignant lesions excised with clear margins}}{\textit{Total number of malignant lesions excised}}\right) \textit{X100\%}$$

OBJECTIVE 3: To evaluate the safety of the ABBI system as a surgical technique for the management of breast lesions

1. Estimated Blood Loss

The safety of the ABBI was evaluated by the amount of estimated blood loss and the frequency and severity of surgical or post-surgical complications.

The amount blood lost during the procedure was estimated from the gauzes used during surgery. According to the Canadian Guidelines for Clinical Practice, blood transfusion is indicated after an acute blood loss greater than 20% of the total blood volume, regardless of the patient's hematocrit. For a 70kg adult, this amounts to approximately 70cc/kg[152-161].

2. Surgical Complications

The incidence of surgical complications was determined by the data abstracted from the surgical report.

OBJECTIVE 4: To describe patient satisfaction with the ABBI;

A survey consisting of 14 multiple choice questions relating to the patients' satisfaction with the ABBI was used. The questionnaire was given to the patients immediately after they left the ABBI room and was completed before leaving the hospital. The questions included in the survey are listed in Appendix 9.

The survey used was developed for the current study using similar questions to those used in other studies on the ABBI. There are no validated standardized questionnaires for the assessment of patient satisfaction with the ABBI. It was decided not to use a general patient satisfaction questionnaire since the items had to be specific to the ABBI. The patient satisfaction results were analyzed descriptively only without the calculation of a score. Therefore, use of a validated tool was not essential.

OBJECTIVE 5: To assess the volume-performance association for the ABBI

In order to assess the volume-performance association and surgeon effect for the ABBI the performance indicators used were diagnostic and therapeutic effectiveness. Diagnostic effectiveness was assessed by the need for re-excision based on the presence of involved macroscopic margins. Therapeutic effectiveness was assessed by the presence of involved microscopic margins for malignant tumors. Therapeutic effectiveness was not assessed for benign tumors since involved microscopic margins reports for the benign lesions are not clinically relevant and are not reported by the pathologist.

The independent variable describing the surgeon was simply a categorical variable with a randomly selected value ranging from 1-3 to

represent each one of the three participating surgeons. In this analysis, for each patient, prior ABBI volume of the surgeon was defined as the number of ABBI procedures that the surgeon had performed prior to the date of the ABBI.

In order to assess the crude association between surgeon and the performance indicators described above the Chi-Square statistic was used. A simple logistic regression model was used to assess the effect of prior ABBI volume on diagnostic and therapeutic effectiveness. Multivariate-logistic regression models were used to asses the independent effect of surgeon and prior ABBI volume on diagnostic and therapeutic effectiveness. The multiple logistic regression models included a dummy variable with two levels representing the surgeon, a continuous variable representing prior ABBI volume and the surgeon x volume interaction term. The interaction term was included to investigate whether there is a difference between surgeons with respect to the volume-performance association.

OBJECTIVE 6: To describe the cost evaluation of the ABBI

Economic evaluation of the ABBI was aimed at assessing whether management of patients with the ABBI results in cost reductions when compared to excisional biopsy with wire localization. The results in the literature have shown that the rate of supplementary surgery for the ABBI to be between 8% and 42% while that for the wire localization

excisional biopsy to be between 17% and 76%[38,39,43,44,125,126,136,138,141,143,145,148-150,162-164]. In the current study we observed a 23.7% rate of involved microscopic margins for the ABBI. This rate was 53% of the 531 patients that underwent a wire localization biopsy that had malignant tumors. These results suggest that therapeutic effectiveness is higher for the ABBI when compared to wire localization biopsy. In consideration of the above, cost-effectiveness analysis would not be required if cost-minimization was demonstrated for the ABBI compared to wire localization excision biopsy.

In the economic analysis only total direct health costs were considered. These included the cost for the ABBI or wire localization excisional biopsy and the cost for any supplemental surgery required. In the current study the supplemental surgery considered was partial mastectomy since this was the only procedure used subsequent to the ABBI or wire localization excisional biopsy. Cost estimates for the ABBI, wire localization excisional biopsy and partial mastectomy were obtained from the costs centers of the participating institutions. The detailed list of the items included in the calculation of these costs is included in Appendix 10. All costs estimates were in 2000 Canadian Dollars.

In order to obtain precise estimates of the need for supplemental surgery the data from studies reporting supplementary surgery for the ABBI and wire localization excisional biopsy in the literature were combined with those obtained in our study. The data

used to produce these estimates are described in Appendix 11. Accordingly the estimated rate for supplemental surgery for the ABBI was 14.9% (95% CI: 12.6% - 17.2%) and that for wire localization was 30.2% (95% CI: 27.7% - 32.8%).

Cost assessment was based on a simulation of a hypothetical cohort of 1,000 patients that underwent the two alternative procedures, specifically the ABBI and wire localization biopsy. For each of the two procedures the point estimate of supplemental surgery rates described above were used. Sensitivity analysis was conducted to determine the possible ranges of total costs for each procedure using the upper and lower 95% confidence intervals limits for the need of supplemental surgery. Accordingly, the worst case scenario was that in which the upper 95% CI limit for supplemental surgery was used for the ABBI (17.2%) and the lower limit (27.7%) was used for the wire localization. The best case scenario was that in which the lower limit was used for the ABBI (12.6%) and the upper limit (32.8%) was used for the wire localization. The two intermediate scenarios were based on using the upper (ABBI: 17.2% and wire localization: 32.8%) and lower (ABBI: 12.62% and wire localization: 27.7%) limits for both alternatives.

3.7 ABBI SURGICAL METHOD DESCRIPTION

A detailed technical description of the ABBI method is presented in appendix 12. This description is included because it may be useful to the reader to appreciate the ABBI procedure.

All ABBI patients had agreed and given their written consent to undergo the procedure. All ABBI biopsies were performed at the day-surgery clinic under local anaesthesia. Prior to the procedure each patient was briefed about the ABBI equipment and was then given a description of the procedure.

3.8 RESULTS

3.8.1 PATIENT ENROLMENT AND CHARACTERISTICS:

This research project enrolled patients since the first year of development and implementation of the ABBI system in the two participating centers. In October 1995 the first two patients were enrolled. Since then, 2 additional patients were operated during the first year (1995), for a total of 4 or 1.5% of the total 262 patients enrolled. In the following years the number of ABBIs performed each year increased progressively. Forty-eight (18.3%) patients were operated on in 1996, followed by 50 (19.1%) in 1997, 60 (22.9%) in 1998, and 80 patients (30.5%) in 1999. The number of ABBI procedures decreased to 14 (5.3%) and 6 (2.3%) in 2000 and 2001 respectively.

Two hundred and sixty-two women (262) with a mean age (SD) of 57.4 (11.5) years ranging from 31 to 83 years who underwent a breast biopsy with the use of the ABBI system were included in this study (Figure 9).

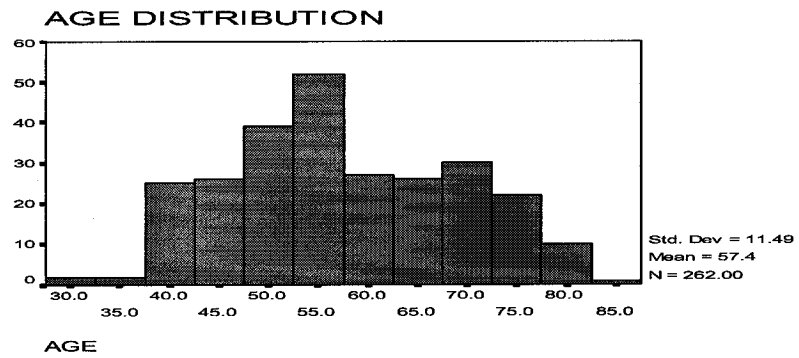


Figure 9: Age distribution of patients submitted to an ABBI

3.8.1.1 Mammographic Indication for the Procedure

The mammographic indication for the diagnostic procedure was microcalcifications for 175 cases (66.8%), a soft tissue nodule for 79 cases (30.2%) and in 8 cases (3.1%) a combination of microcalcifications and soft tissue nodules.

3.8.1.2 Description of Lesions and Surgical Approach

The distribution of the location of the lesion in the breast is described in figure 10. The majority of the excised lesions (56.1%) were

located at the left upper outer quadrant, followed by 10.7% in the right upper outer quadrant of the breast.

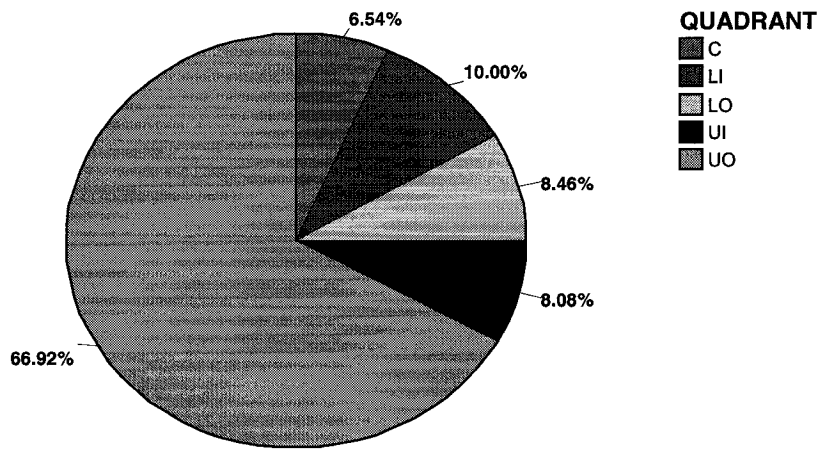
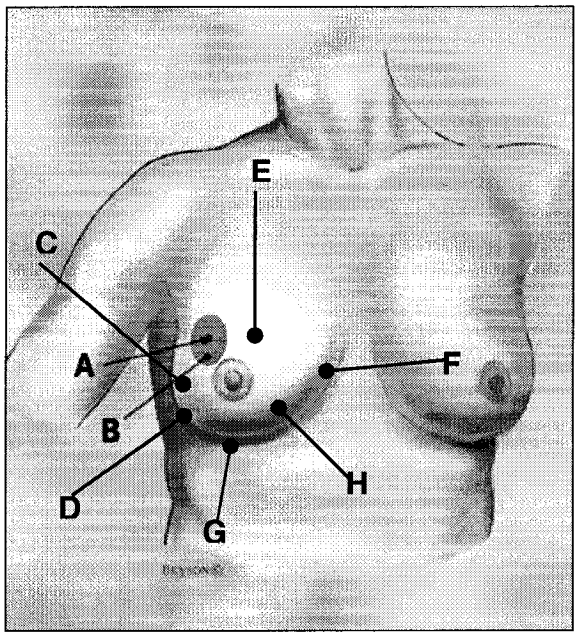


Figure 10: Distribution of the location of the lesion in the breast

Excision surgical approach refers to the side of the breast at which the incision will be performed for the biopsy. The choice of excision approach was depended on the distance between the point of incision and the target lesion (Figure 11 and 12). The approach that permitted the removal of less breast tissue without jeopardizing the complete excision of the target lesion within surgically safe margins was chosen. The most frequent approach was lateral, used in 117 (44.7%) of the patients. In 77 (29.4%) patients the inferior approach was used and the superior was used in 28 (10.7%) cases, and the medial in 22 (8.4%). In the remaining cases a combination of different approaches was used such as oblique/inferior and oblique/medial. The lateral approach was

preferred because it offers greater freedom and ease of movement for the surgeon.



A = dark area indicates tumor
B = light pink highlighted area indicates tissue removed at lumpectomy
C = lateral approach
D = oblique-inferior approach
E = superior approach
F = medial approach
G = inferior approach
H = oblique-medial approach

Figure 11: Description of possible excision approaches

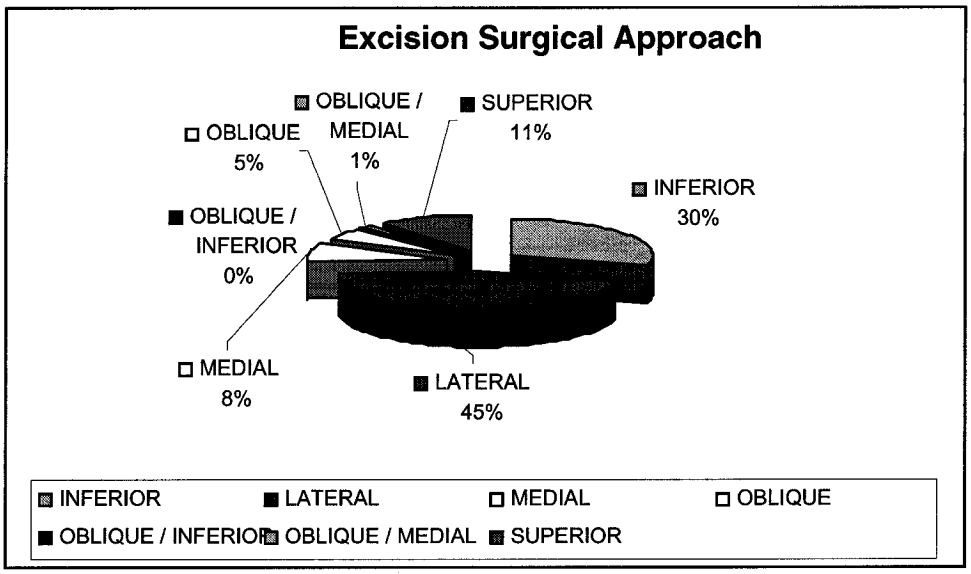


Figure 12: Distribution of excision surgical approaches used in the study

3.8.1.3 Breast Compression

The compression of the breast ranged from 28mm to 89mm with a mean (SD) of 52.7mm (11.4). The depth of the most superficial lesion excised was 7mm. from the skin and that of the deepest lesion was 45mm. with a mean (SD) depth of 29.7 mm (8.3). All tumors were excised without any damage to the opposite side of the breast (within safe posterior margins).

3.8.1.4 Tumor Size

The length of the largest diameter of the tumor was recorded as an indicator of tumor size. As measured by digital mammography, the tumor size ranged between 1mm and 30mm with a mean (SD) of 8.5mm (4.9). The majority of the tumors (43.9%) ranged between 5.1 and 10.0 mm. in diameter. Of the remaining, 32.4% ranged between 1.0mm and 5.0 mm, 16.4% from 10.1mm to 15 mm and 6.1% from 15.1mm to 20.0 mm. Even though the inclusion criteria restricted the size of the tumor to 20 mm or less, in 2 cases (1.2%), the calcifications were widely spread reaching a total size of greater than 20mm. In these cases, the ABBI was performed for purely diagnostic purposes and was recorded as such. These cases were not included in the analysis.

The excised specimen measured 20 mm. or less in diameter and from 15 to 35 mm. in length, with a mean (SD) volume of excised breast tissue of 40cc (36). The mean (SD) volume of excised breast tissue from

20 biopsies with wire localization excisional biopsy excisional biopsy was 102cc (59).

3.8.2 MEASURES OF EFFECTIVESS:

3.8.2.1 Evaluation of the diagnostic effectiveness of the ABBI for the management of breast disease

Among the 260 specimens excised, 259 contained the target lesion for an overall diagnostic effectiveness of 99.6% with 95% confidence intervals (97.02, 99.97). In one case no lesion was identified in the specimen image or in the post-biopsy mammogram. Histological analysis of the specimen diagnosed fibrocystic breast tissue. Immediate re-excision was required in 42 (15.6%) of the 260 cases.

The data in table 2 describe the diagnostic effectiveness by lesion location. These results show that that the rate of successful lesion excision was not affected by the location of the lesion (chi-square value 18.819, p=0.403).

QUADRANT	MICROMARGIN n=259 (99.6%)		Total
	CLEAR	INVOLVED	
Central	16 (6.2%)	1 (0.4%)	17
Lower inner	23 (8.9%)	3 (1.2%)	26
Lower outer	18 (6.9%)	4 (1.5%)	22
Upper inner	20 (7.7%)	1 (0.4%)	21
Upper outer	162 (62.5)	11 (4.2%)	174
Total	**239 (92.3%)**	**20 (7.7%)**	**259**

Table 2: Clarity of micromargins by lesion location

3.8.2.2 Evaluation of the therapeutic effectiveness of the ABBI for the management of breast cancer

3.8.2.2.1 Histological Distribution of Excised Margins

Therapeutic effectiveness is defined as the proportion of lesions excised within clear micromargins. In order to appreciate the overall therapeutic effectiveness of the ABBI, verification of the histological assessment of the lesion and the microscopic margins are important.

In total, of the 260 excised tumors (184 benign and 76 malignant) 240 were excised within clear margins. Of the 184 benign tumors, 182 (98.9%) were excised within clear margins. Therefore, the overall therapeutic effectiveness of the ABBI to adequately excise tumors within clear margins is 92.3% with 95% confidence Intervals between 89.2% and 95.6%. Of the 76 malignant tumors, 58 (76.3%) (CI 74.9%, 78.3%) were excised within clear surgical margins. (Figure 13). However, the

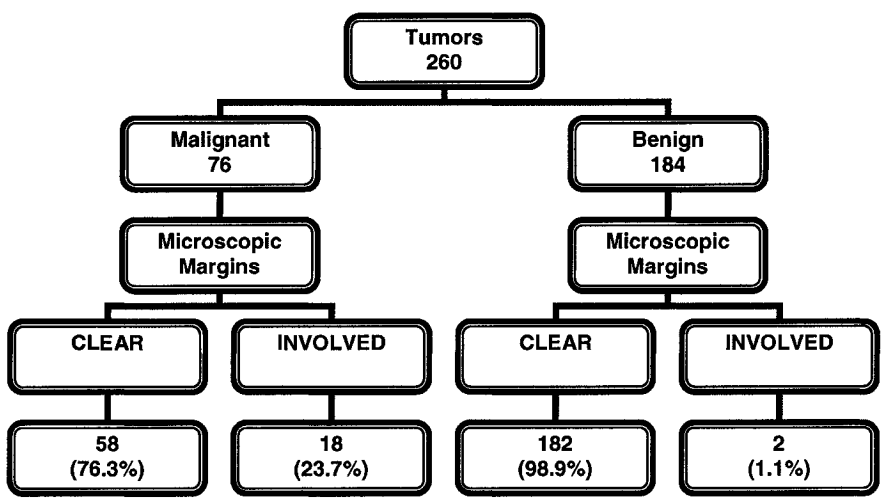


Figure 13: Microscopic margins of excised tumors

therapeutic effectiveness is only relevant for malignant tumors. As mentioned earlier, this was 76.3% with 95% confidence intervals between 74.9% and 78.3% (Figure 14).

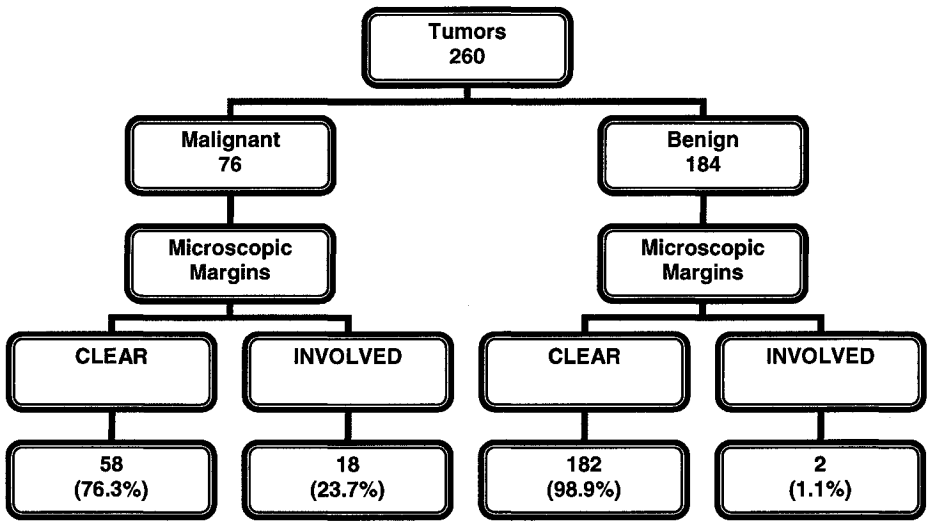


FIGURE 14: Histologic distribution and microscopic margins of excised tumors

The distribution of the histological assessment of the excised tumors is described in tables 3 and 4. Of the 260 tumors excised, 184 (70.2%) were benign tumors and 76 (29.8%) were malignant. Of the 184 benign tumors, 112 (60.9%) were diagnosed as fibrocystic changes, 54 (29.3%) were mainly fibroadenomas, adenosis, fat necrosis, fibrosis, papillomas, sclerosing adenosis and cysts, and 18 (9.8%) were diagnosed as atypic hyperplasia (a potentially pre-malignant condition requiring a more careful follow-up than other benign tumors).

Of the 76 malignant lesions excised, 21 (27.6%) were intraductal (DCIS) carcinoma and 36 (47.4%) infiltrating (invasive) ductal cell carcinomas. There were 19 (25.0%) mixed cancers of which, 17 (22.4%) were infiltrating ductal carcinomas with intraductal components and 2 (2.6%) lobular cell in situ (LCIS) carcinomas with focal Lobular infiltration (Table 3 and 4).

BENIGN TUMORS	Frequency	Category (%)	Total %
Fibrocystic breast	112	60.9	43.1
Benign tumour	54	29.3	20.7
Atypic hyperplasia	18	9.8	6.9

Table 3: Histological distribution of the excised tumors

MALIGNANT TUMORS	Frequency	Category (%)	Total %
DCIS	21	27.6	8.1
Infiltrating Ductal Ca	36	47.4	13.8
DCIS + Infiltrating Ductal Ca	17	22.4	6.5
LCIS + Infiltrating Lobular Ca	2	2.6	0.8
Total	**260**	**100**	**100**

Table 4: Histological distribution of the excised tumors

Complete excision is essential mainly for malignant tumors in order to avoid residual malignancy which may lead to metastasis and recurrent disease. The effectiveness of the ABBI to excise malignant tumors within clear microscopic margins (at least 1mm healthy breast tissue surrounding the tumor), defined as therapeutic effectiveness, was 76.3% (95% CI 66.7%, 85.9%) (Figure 15). Eight (23.7%) of the 36 infiltrating ductal carcinomas were excised within involved microscopic margins.

Infiltration of the surgical margins was detected in 4 (19.0%) of the 21 DCIS, and 6 (35.3%) of the 17 mixed tumors. All LCIS were sufficiently excised free of tumor.

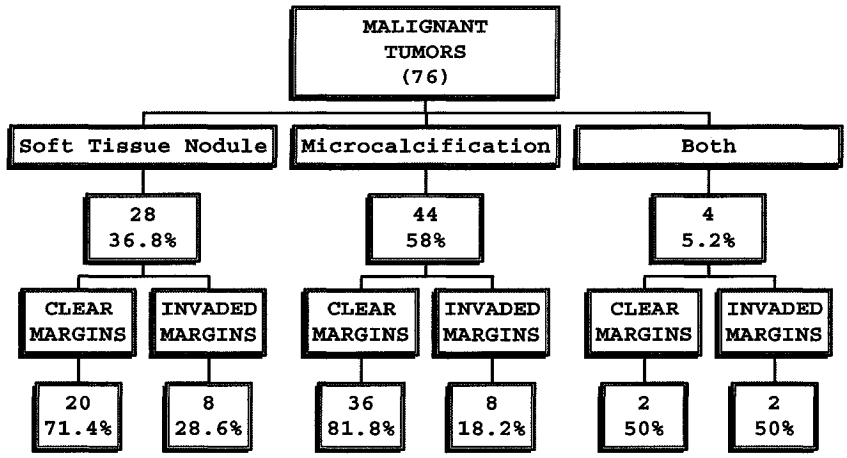


Figure 15: Therapeutic effectiveness of the ABBI to excise malignant tumors

3.8.2.2.2 Therapeutic Follow-Up

Of the 76 patients with a malignant tumor, 21 (27.6%) required additional surgical treatment. More specifically, of the 36 women diagnosed with infiltrating ductal carcinomas, 9 (25%) underwent a supplementary partial mastectomy combined with axillary lymph node dissection. However, in all nine of these cases the original tumor excision was shown to be complete and no residual tumor was found. Four (19.0%) of the 21 patients with DCIS were submitted to partial mastectomy. Residual tumor was found in three (14.3%) of the 21 cases. Finally, eight (47.1%) of the 17 mixed tumors with mixed infiltrating ductal carcinomas and DCIS were submitted to a supplementary partial

mastectomy, of which 2 had residual cancer. None of the two mixed infiltrating lobular carcinomas with LCIS required further excision. Overall, 5 (23.8%) of the 21 patients who had supplementary surgery had residual malignancy in the surrounding breast tissue excised. The remaining 55 (72.4%) of the 76 patients with malignant tumors were submitted to a combination of radiotherapy, chemotherapy and/or Tamoxifen. Supplementary mastectomy was not required for benign tumors since there is no known possibility of recurrence in case of residual disease.

3.8.2.3 Evaluation of the safety and tolerability of the ABBI system as a surgical technique for the management of breast tumors

Safety was assessed by total blood loss during surgery and incidence of complications. The total blood loss during surgery was estimated from the gauzes consumed and ranged from 1 to 200 cc. (mean 26.3 cc.) which is below the accepted limits.

The following peri-operative complications occurred: For two patients, the cannula malfunctioned before reaching the target in the breast. In both cases the gear was drawn off the breast manually and the tumor was excised under direct vision. One of these two patients had mentioned an increased sensitivity in the neck and shoulder due to a previous accident complained of pain.

For one patient, the T-crossbar did not deploy. In this case the specimen was not securely attached in the cannula of the ABBI. When the cannula was removed from the breast the specimen remained in the cavity attached only at the posterior breast tissue, from where it was cut and excised under direct vision.

For one patient no specimen was retrieved with the ABBI during the first attempt but the second attempt was successful. The most possible explanation for this is that the T-crossbar may not have deployed completely so the specimen was only partially attached to the cannula, which made it possible to remove the specimen with the second attempt.

Two women presented with greater than usual bleeding during the ABBI followed by difficulty with haemostasis during the closure of the surgical cavity. After the bleeding was controlled and the cavity was sutured, both women remained lying supine on the LoRad table with a sandbag on the breast for 30 minutes. A sandbag is usually made of cotton and filled with a heavy and fine material such as sand. It is used as a way to apply pressure in the bleeding area to facilitate blood clotting and haemostasis.

One patient complained of inability to further remain in the supine position. The procedure was terminated before the post-biopsy mammogram and the patient was allowed to turn in the supine position. There was no case of loss of conscience or vomiting.

In the post-operative phase the following complications or discomforts were reported. Three women presented post-operatively with mild wound infections which were successfully managed with partial removal of sutures and saline bathing. One patient developed a delayed haematoma which was drained and the incision was re-sutured. Three more patients developed a mild haematoma which was treated conservatively with pressure and cold compresses.

3.8.2.4 Description of patient satisfaction with the ABBI experience

Because the fourth objective was added in the study during the final 3 years, only the last 100 patients were asked to participate in a brief survey that consisted of 13 questions and was administered immediately after the procedure and during the brief recovery period before the patient was permitted to leave the clinic. The survey responses are summarized in the following table. The detailed survey is presented in Appendix 9.

Of the 100 patients who answered the questionnaire, the majority, 85 % (95% CI 78% - 92%) chose the specific clinic (medical center) because they were referred there by their treating physician. Only 5% (95% CI 0.7% - 9.3%) admitted that they had an "excellent" understanding of their therapeutic options whereas 65% (95% CI 55.7% - 74.3%) rated their knowledge as "very good". On the other hand, 45%

(95% CI 35.2% - 54.8%) and 25% (95% CI 16.5% - 33.5%) of these patients reported that their knowledge of the differences between the ABBI was "very good" and "moderate" respectively. Most patients, 65% (95% CI 55.7% - 74.3%) selected the ABBI because they trusted their physician and 20% (95% CI 12.2% - 27.8%) because they preferred local rather than general anaesthesia. The patients' understanding of the advantages and disadvantages of the ABBI compared to other options was "very good" for 33% (95% CI 23.8% - 42.2%), "good" for 30% (95% CI 21.0% - 36.0%) and "moderate" for 22% (95% CI 13.9% - 30.1%).

The waiting time for the procedure ranged from 1-8 weeks; 45% (95% CI 35.2% - 54.8%) of patients waited for 1-2 weeks, 35% (95% CI 25.7% - 44.3%) for 2-4 weeks and 20% (95% CI 12.2% - 27.8%) 5-8 weeks. The majority of the patients (51% / 95% CI 41.2% - 60.8%) received their biopsy results 1-2 weeks after the procedure and the remaining 49% (95% CI 39.2% - 58.8%) between 2-4 weeks post-surgery.

Of the 100 patients who responded to the questionnaire, 40% (95% CI 30.4% - 49.6%) rated their level of general satisfaction with the facility as "very good", 35% (95% CI 25.7% - 44.3%) as "excellent" and 20% (95% CI 12.2% - 27.8%) as "good".

Comfort during the procedure was rated as "very good" by the majority (57%) (95% CI 47.3% - 66.7%) of the patients. The remaining patients were divided between "excellent" for 11% (95% CI 5.8% -

17.5%), "good" for 12% (95% CI 5.6% - 18.4%) and "moderate" for 13% (95% CI 6.4% - 19.6%). However, their level of comfort after the procedure was rated by 63% (95% CI 53.5% - 72.5%) as "very good" and by 21% (95% CI 13.0% - 29.0%) as "good".

The majority of the patients (51%) (95% CI 41.2% - 60.8%) reported a "very good" level of satisfaction with the actual procedure while 23% (95% CI 14.8% - 31.2%) reported their level of satisfaction as "excellent" and 18% (95% CI 10.5% - 25.5%) as "good". Eighty percent (95% CI 72.2% - 87.8%) of these 100 patients had no regrets for choosing the ABBI and 49% (95% CI 39.2% - 58.8%) returned to normal activity within the same day.

3.8.2.5 Evaluation of the volume-performance association for the ABBI

3.8.2.5.1 Diagnostic Effectiveness as Performance Indicator:

Table 5 shows the re-excision rates for each one of the three surgeons participating in the study. Although surgeon #2 had the highest re-excision rate and surgeon #3 the lowest, this difference did not achieve statistical significance (Chi-Square = 0.659, P = 0.719).

SURGEON	Re-Excision			
	No		Yes	
	N	%	N	%
1	115	83.3%	23	16.7%
2	41	80.4%	10	19.6%
3	61	85.9%	10	14.1%

Table 5: Re-Excision rates by Surgeon:

Table 6 summarizes the results of the simple logistic regression model for the evaluation of the association between prior ABBI volume and diagnostic effectiveness. In this model the dependent variable was the need for re-excision defined as 1= yes and 0 = no. These results show that there is a significant association between prior ABBI volume and performance as measured by the surgeon's ability to completely excise the target tumor. The logistic regression odds ratio of 0.975 was significant ($P<0.001$) and shows that with every additional ABBI performed the risk for re-excision decreases by a factor of 0.025. It should be noted that although the estimated odds ratio is relatively small, it measures the effect of volume as a continuous variable.

Variable	Parameter estimate(B)	S.E.	P – Value.	Odds Ratio	95 % CI for Odds Ratio	
Prior ABBI Volume (continuous)	-0.026	0.003	0.001	0.975	0.968	0.981

Table 6: Simple Logistic Regression Model Results (Diagnostic Effectiveness)

Figure 16 describes the estimated probability (risk) for re-excision by prior ABBI volume. The probability for re-excision was estimated from the odds ratio obtained using the logistic regression parameter for each case in the sample. The following formulae were used:

$$Odds\ Ratio\ (OR) = e^{volume \times -0.026} \qquad Probability = OR / (1+OR)$$

These results show that for a re-excision risk of 20% approximately 40 – 50 procedures must have been performed by the surgeon. This is however, an exploratory analysis demonstrating the association between volume and performance. Establishing performance – risk thresholds will require further analysis and consideration of patient risk tolerance as well as economic impact.

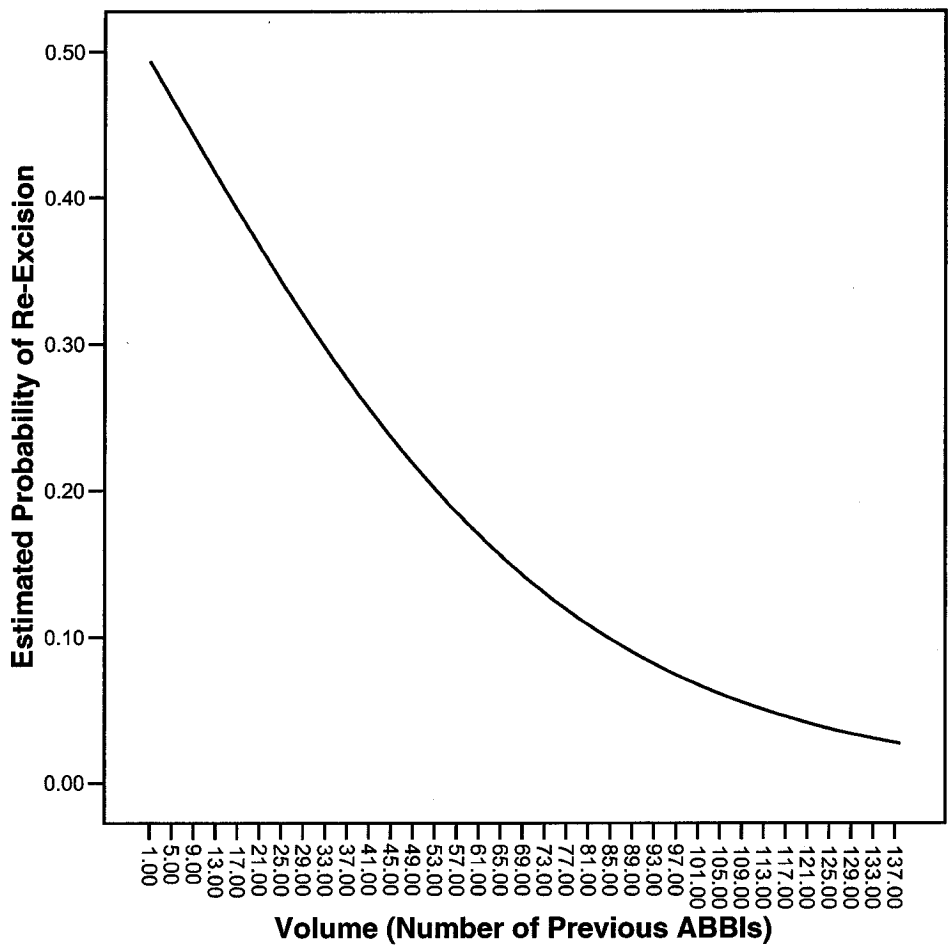


Figure 16: Estimated probability of re-excision by previous ABBI volume:

Table 7 summarizes the results of the multi-variate logistic regression models for diagnostic effectiveness. These results show that both the surgeon and prior ABBI volume have a significant association with the need for re-excision. For the surgeon effect, more precisely, the significant effect was noted between surgeon # 3 and surgeon # 2.In addition a significant surgeon – prior ABBI volume interaction effect was observed. This would suggest that an analysis assessing the prior ABBI volume effect stratified by surgeon would be required.

Variable:	Parameter estimate (B)	S.E.	P – Value.	Odds Ratio	95 % CI for Odds Ratio	
Prior ABBI Volume	-0.037	0.009	0.001	0.964	0.947	0.980
Overall Surgeon Effect			0.012			
Surgeon 3 vs. 2	-1.266	0.436	0.004	0.282	0.120	0.664
Surgeon 3 vs. 1	-0.401	0.654	0.539	0.669	0.186	2.411
Surgeon * volume			0.005			
Surgeon 3 vs. 2 by volume	0.032	0.010	0.002	1.032	1.012	1.054
Surgeon 3 vs. 1 by volume	-0.006	0.028	0.816	0.994	0.941	1.049

Table 7: Multi-Variate Logistic Regression Model Results (Diagnostic Effectiveness)

Table 8 summarizes the results of the simple logistic regression models assessing the association between prior ABBI volume and diagnostic effectiveness stratified by surgeon. These results show that although the prior ABBI volume effect was significant for all surgeons, the strongest effect was observed for surgeon #2.

SURGEON	Variable	Parameter estimate(B)	S.E.	P – Value	Odds Ratio	95 % CI for Odds Ratio	
1	Volume	-0.020	0.003	0.001	0.980	0.973	0.986
2	Volume	-.0057	0.015	0.001	0.944	0.917	0.973
3	Volume	-0.037	0.009	0.001	0.964	0.947	0.980

Table 8: Stratified Simple Logistic Regression Model Results (Diagnostic Effectiveness)

3.8.2.5.2 Therapeutic Effectiveness as Performance indicator:

Therapeutic effectiveness was evaluated only for the malignant tumors.

Table 9 describes the microscopic margin assessment by surgeon. These results show that although surgeon # 1 had the highest rate of

involved margins, the difference was not statistically significant (Chi – Square: 1.535, P = 0.646).

SURGEON	Microscopic Margins				Total
	Clear		Involved		
	N	%	N	%	
1	33	71.7%	13	28.3%	46
2	12	80.0%	3	20.0%	15
3	13	86.7%	2	13.3%	15

Table 9: Microscopic margin results by surgeon:

Table 10 summarizes the results of the simple logistic regression model for the evaluation of the association between prior ABBI volume and therapeutic effectiveness. In this model the dependent variable was the presence of involved margins defined as 1= yes and 0 = no. These results show that there is a significant association between volume and this performance indicator. The logistic regression odds ratio of 0.980 was significant (P<0.001) and shows that with every additional ABBI performed the risk for re-excision decreases by a factor of 0.020.

Variable	Parameter estimate(B)	S.E.	P – Value.	Odds Ratio	95 % CI for Odds Ratio	
Prior ABBI Volume (continuous)	-0.021	0.005	0.001	0.980	0.970	0.989

Table 10: Simple Logistic Regression Model Results (Diagnostic Effectiveness)

Figure 17 describes the estimated probability (risk) for having an involved margin by prior ABBI volume. The probability an involved margin was estimated from the odds ratio obtained using the logistic

regression parameter for each case in the sample. The following formulae were used:

$$Odds\ Ratio\ (OR) = e^{volume \times -0.021} \qquad Probability = OR / (1+OR)$$

These results show that for an involved margin rate of 20% approximately 65 procedures must have been performed by the surgeon. This is however, an exploratory analysis demonstrating the association between prior ABBI volume and performance. Similarly with the diagnostic effectiveness, establishing performance – risk thresholds will require further analysis and consideration of patient risk tolerance as well as economic impact.

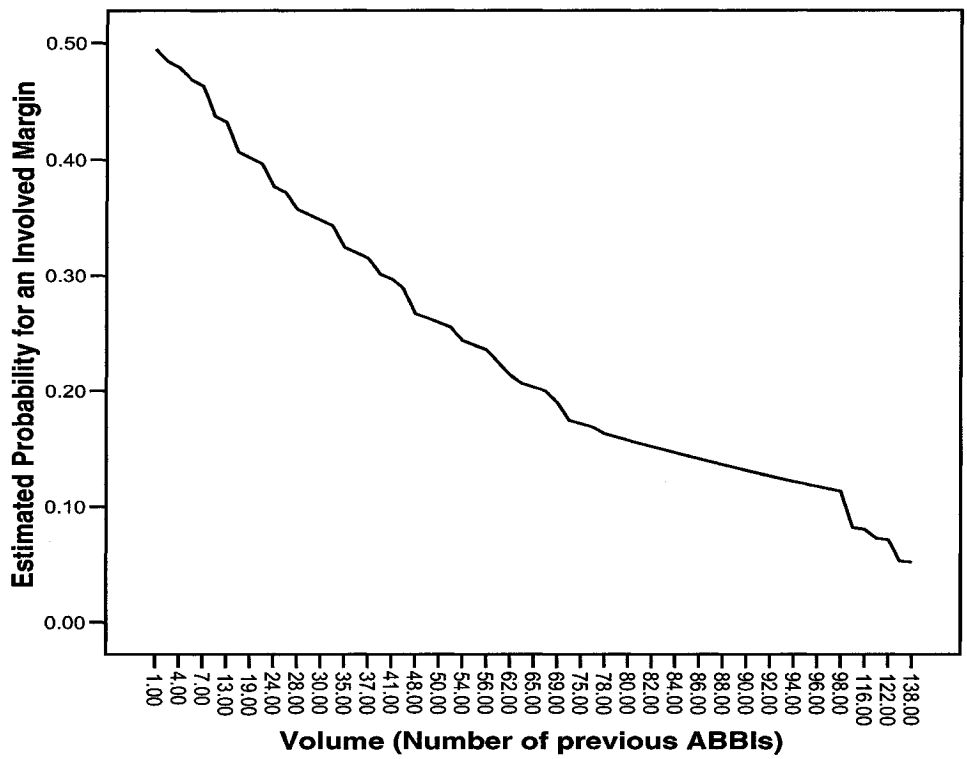


Figure 17: Estimated probability of involved margin by previous ABBI volume

Table 11 summarizes the results of the multi-variate logistic regression models for therapeutic effectiveness. These results show that only prior ABBI volume had a significant association with the risk for involved having microscopic margins. The association for surgeon was not significant and the surgeon-volume interaction effect was also not significant.

Variable:	Parameter estimate(B)	S.E.	P – Value.	Odds Ratio	95 % CI for Odds Ratio	
Prior ABBI Volume	-0.048	0.022	0.029	0.953	0.913	0.995
Overall Surgeon Effect			0.302			
Surgeon 3 vs. 2	1.071	0.852	0.208	2.919	0.550	15.488
Surgeon 3 vs. 1	0.433	1.592	0.368	4.191	0.185	94.961
Surgeon * volume			0.375			
Surgeon 3 vs. 2 by volume	0.019	0.025	0.440	1.019	0.971	1.071
Surgeon 3 vs. 1 by volume	-0.057	0.064	0.378	0.945	0.833	1.072

Table 11: Multi-Variate Logistic Regression Model Results (Therapeutic Effectiveness)

Table 12 summarizes the results of the simple logistic regression models assessing the association between prior ABBI volume and therapeutic effectiveness stratified by surgeon. This analysis was conducted for descriptive purposes although it may have not been required since a significant surgeon-volume interaction effect was not detected. These results show that although the volume effect was significant for all surgeons, the strongest effect was observed for surgeon #2.

SURGEON	Variable	Parameter estimate(B)	S.E.	P – Value.	Odds Ratio	95 % CI for Odds Ratio	
1	Volume	-0.016	0.005	0.001	0.984	0.975	0.994
2	Volume	-0.060	0.027	0.024	0.942	0.894	0.992
3	Volume	-0.048	0.022	0.029	0.953	0.913	0.995

Table 12: Stratified Simple Logistic Regression Model Results (Therapeutic Effectiveness)

3.8.2.6 Description of the cost evaluation of the ABBI

The results of the economic evaluation comparing the ABBI to wire localization biopsy are summarized in Table 13. These results show that on the average the ABBI would result in a cost reduction of $5,352 CAD (2000). Under the worst case and best case scenarios using the ABBI would result in a cost reduction of $4,847 CAD (2000) and $5,853 CAD (2000) respectively. Intermediate cost reductions were $5,703 CAD (2000) and $5,627 CAD (2000).

In consideration of the observed lower total cost or cost-minimization and higher rates of therapeutic effectiveness for the ABBI in comparison to the wire localization biopsy, further economic evaluation based on cost-effectiveness was not pursued.

Scenario:	Point Estimate		Worst		Intermediate (Low)		Intermediate (High)		Best	
Procedure:	**ABBI**	**WL**	**ABBI**	**WL**	**ABBI**	**WL**	**ABBI**	**WL**	**ABBI**	**WL**
Number of Cases	1,000	1,000	1000	1000	1000	1000	1000	1000	1000	1000
Cost per Case	$653	$2,027	$653	$2,027	$653	$2,027	$653	$2,027	$653	$2,027
Total Cost For 1,000 Cases	$653,000	$2,027,000	$653,000	$2,027,000	$653,000	$2,027,000	$653,000	$2,027,000	$653,000	$2,027,000
Supplemental Surgery Rate	14.9%	30.3%	17.2%	27.8%	12.7%	27.8%	17.2%	32.8%	12.7%	32.8%
Number with Supplemental Surgery	97	614	112	564	82	563	112	664	83	665
Cost per case of Supplemental Surgery	$7,697	$7,697	$7,697	$7,697	$7,697	$7,697	$7,697	$7,697	$7,697	$7,697
Total Cost for all Supplemental Surgery	$748,895	$4,727,351	$864,496	$4,337,306	$638,320	$4,337,306	$864,496	$5,117,397	$638,320	$5,117,397
Total for Surgical Management of 1,000 Patients	$1,401,895	$6,754,351	$1,517,496	$6,364,306	$1,291,320	$6,364,306	$1,517,496	$7,144,397	$1,291,320	$7,144,397
Total Cost Per Patient	$1,402	$6,754	$1,517	$6,364	$1,291	$6,364	$1,517	$7,144	$1,291	$7,144
Cost Difference (ABBI – WL)	**-$5,352**		**-$4,847**		**-$5,703**		**-$5,627**		**-$5,853**	

Table 13: Summary of Cost Analysis of ABBI versus Wire Localization Biopsy: WL = Wire Localization Biopsy

3.9 DISCUSSION

National mammographic screening programs for the early detection of breast cancer have led to a continuously increasing number of new breast cancer cases detected each year. According to the Canadian Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer, once an abnormality is detected in a screening mammogram a combination of further radiologic work-out and clinical examination is initiated. The objective is to acquire a more accurate description of the abnormality and to estimate the level of suspicion or risk for cancer[20]. The decision on the appropriate management is based on the estimated level of risk of the mammographic finding and is taken after discussion and agreement between the treating physician and the patient. Depending on the level of risk (Category 1-4) and the preference of the patient, management options may range from observation with a 6-month follow-up mammogram, incisional biopsy (tissue sampling) or excisional biopsy (complete removal of the lesion).

Once the decision is made for complete removal of the lesion, the choice of surgical technique is based on whether the abnormality is palpable or non-palpable. For non-palpable lesions, the current standard surgical technique is wire localization excisional biopsy. This technique combines image-guided localization and surgical excision of the lesion with a conventional open biopsy. The advantages of wire localization excisional biopsy are the excision of a specimen that is sufficient for an

accurate histopathological diagnosis, the minimal post-operative complications, the removal of less breast tissue than partial mastectomy, and the shorter duration of hospitalization of the patient[41-44].

A disadvantage of wire localization excisional biopsy is that it is a repetitive multiple step process involving radiology and surgery until the excision is considered complete. In approximately 20-25% of the cases the lesion is not found in the initial specimen and in 59.4% of the cases the surgical margins are not clear of malignancy[35-40,52-99,116-124]. This results in a longer duration of surgery and anaesthesia and a larger amount of breast tissue removed (mean volume 102cc)[27-34,81,84,100-124]. Therefore, the use of wire localization as a diagnostic tool is acceptable but not ideal.

Microscopic assessment of the excised specimen has shown a 40-59% false negative rate for specimens with clear macroscopic margins. Approximately 59.4% of patients require further local surgery[23,31-40,46,47]. Based on these results, the therapeutic utility of wire localization biopsy is questionable[47,48].

Because of the disadvantages of wire localization excisional biopsy an alternative minimally invasive image-guided excisional biopsy technique, the ABBI, has been developed. The ABBI was evaluated in this study. The diagnostic effectiveness of the ABBI in the series of 260 patients was 99.6%. This was similar to the reported 98% for wire

localization excisional biopsy[265]. However, re-excision was required in 15.6% of the patients who underwent an ABBI compared to 20-25% as reported in the literature for wire localization excisional biopsy[35-40,52-99,116-124,146].

Both the ABBI and wire localization excisional biopsy are considered microinvasive since they aim to excise the tumor with clear surgical margins and with the removal of the least amount of healthy peripheral breast tissue as possible. Breast conservation is therefore an important consideration in the management of breast disease at this stage.

Given that the overall effectiveness as diagnostic procedures of both techniques is similar, the size of the excised specimen becomes an important consideration. The mean volume of the specimen excised with the ABBI was 40.2cc versus 102cc for the 531 wire localizations performed in the same hospitals during the same time period and by the same surgeons. Clearly the ABBI achieved a similar diagnostic effectiveness as the wire localization biopsy with a smaller amount of tissue excised.

In the current study, the therapeutic effectiveness of the ABBI was 76.3% as compared to 53% for the 531 wire localization biopsies reviewed. As reported in the literature, the probability of invaded margins after a wire localization excisional biopsy ranges from 29.5% to 79% with a mean of 59.4%. Nevertheless despite this finding the 24.7% probability

of involved microscopic margins is too high for the technique to be considered as a therapeutic procedure for breast cancer. Based on these results both the wire localization excisional biopsy and the ABBI should not be used as therapeutic interventions.

Another important factor for the assessment of the therapeutic effectiveness of a microinvasive surgical technique for breast cancer is the requirement for supplementary surgery and the probability of residual disease found in the peripheral breast tissue excised. In the current study, the rate of supplementary surgery for the ABBI patients was 27.6% compared to 53% for the 531 wire localization patients. Residual malignancy was found in 23.8% of the post-ABBI patients compared to 48% of the post wire localization excisional biopsy patients.

The complications reported with the ABBI during the current study were minimal. The technique was well tolerated by most patients with 51% and 23% reporting good and excellent level of satisfaction with the procedure respectively.

The results of this study as reported above have shown that the diagnostic effectiveness of the ABBI is similar to that of the wire localization excisional biopsy. With respect to therapeutic effectiveness the ABBI is superior when compared to wire localization excisional biopsy, although none of the techniques is ideal. Consequently, cost effectiveness is an important consideration for the implementation of the technique.

Comparison of the direct health costs of the two techniques shows that, on the average, the ABBI may result in a cost reduction of $5,352 CAD per patient. This would be associated with no loss in diagnostic effectiveness and potential increase in therapeutic effectiveness.

Based on the above the continuation of research aimed at improving the therapeutic effectiveness of the ABBI by reducing the percentage of tumors excised within involved microscopic margins is justified.

A significant surgeon effect and volume - performance association was observed in the current study. This would suggest that adequate training and experience of the surgeon would be required for achieving the maximum benefits from the ABBI. From the patient and societal perspective this is an important finding since it suggests that the effectiveness of the procedure will be influenced by the surgeon's training and experience. Consequently, the establishment of specialized centres with high volume of cases and properly trained surgeons may be the appropriate approach for implementing the ABBI. Indirectly, this may explain why the ABBI has not been presently accepted in many centers. The requirement for additional training and understanding of stereotactic and computerized technology for the successful practice of the ABBI may be an obstacle to its general acceptance.

The results of the current study are in agreement with the published literature with respect to all outcomes measured except for the clarity of

microscopic margins. The studies in the literature report rates of involved margins between 57% and 95% as compared to 24% in the current study. A possible explanation for this discrepancy is that all three surgeons participating in the current study have extensive experience in breast cancer surgery and are experts in micro-invasive surgery of the breast. The expertise of the surgeons providing data for the other studies is not known.

The weaknesses of this study are that it is partially retrospective and non-randomized. Data collected retrospectively may be affected by recall bias and inaccuracy of information in the hospital charts. As a non-randomized trial selection bias may have operated by which the patients that selected the ABBI may be different from those that opted to have the ABBI. Selection bias may have also operated when the surgeons solicited patients to be enrolled in the study. This may have happened if the surgeons selected patients with a higher likelihood of having a better outcome with the ABBI. An additional potential problem with the current study may be that it enrolled patients over a five-year period with surgeon experience changing from naïve to very experienced. As a result, the leaning curve effect has biased the results and consequently under-estimating the effectiveness of the ABBI.

The strengths of the study include the fact that it took place in multiple centers using data from three different surgeons. This improved the possibility of generalization of the results to more than one surgeon.

In addition, by using patients treated by more than one surgeon the study provide the opportunity to assess the surgeon effect. Furthermore, by studying the ABBI from its initial implementation the volume-performance effect was evaluated. This was an original and very important component of the current study.

Although recall and ascertainment bias may have operated in the retrospective part of the study, the outcome measures for both retrospective and prospective parts of the study, specifically diagnostic and therapeutic effectiveness, were based on objective assessments conducted by radiologists and pathologists. The data for these outcomes were obtained from surgical, radiological and histopathology results reported by highly trained and experienced professionals who were not aware of the study. The extent and potential impact of selection bias could not be accurately assessed in this observational non-randomized study. However, the current study was aimed at assessing real-life effectiveness. In a real-life setting both the surgeon and patient will have an active role in deciding whether or not the ABBI will be used. This is very different from a randomized controlled trial where the treatment selection is random and not affected by the surgeon. In addition, in the real-life setting, the surgeon plays typically will selectively offer a procedure only to those patients that have a higher likelihood of success. Therefore, the current study by its observational nature simulates real-life

settings and the results can be generalized to routine clinical practice when compared to those obtained in controlled clinical trials.

3.10 CONCLUSION:

The results of the current study demonstrate that the ABBI is a safe and well tolerated and cost effective microinvasive surgical procedure which offers a higher success rate for clear microscopic margins, with less breast tissue excised, lower requirement for supplementary surgery and less residual tumor in the supplemental peripheral breast tissue removed. Given the significant volume-performance association and the better therapeutic effectiveness of the ABBI as compared to the wire localization biopsy, a well organized training program may help improve the therapeutic effectiveness and increase the practice of the ABBI in the management of breast disease in Canada. Establishment of highly specialized centers offering this procedure would maximize the benefit and reduce costs even more.

The following sections include a brief description of the anatomy of the lymphatic system surrounding the breast with emphasis on the process for cancer metastasis. This introduction is useful for the reader to understand the importance of lymph node assessment for breast cancer and the potential impact of lymphoscintigraphy guided biopsy that is evaluated in the current study.

4 INTRODUCTION

4.1 LYMPHATIC DRAINAGE OF THE BREAST

Once breast cancer has been confirmed by histological or cytological testing, further management directly depends on the stage of the disease. Cancer staging is determined by the extent of disease in regional or local tissues or organs. The single most important predicting factor for long term prognosis in breast cancer is lymph nodes metastasis. Hence, accurate knowledge of the lymphatic drainage of the breast is essential for the comprehension of breast cancer staging.

4.1.1 LYMPH FLOW AND DRAINAGE OF THE BREAST

Understanding of the lymphatic drainage of the breast is essential for the proper appreciation of the importance of sentinel lymph nodes. Metastasis occurs predominantly via lymphatic routes. Contrary to the

blood circulation, normal lymphatic flow is unidirectional and has preferential flow from the periphery toward the right side of the heart. In inflammatory disease or cancer, the lymph flow is obstructed and lymphatic flow is reversed. This is detected microscopically as metastases within the lymphatic flow known as endolymphatic metastases. This obstruction and reversal of lymphatic flow is responsible for neoplastic growth in local and regional sites distant from the primary malignancy.

Metastasis begins with the local invasion of the surrounding tissue by either single or clustered malignant cells from the primary tumor and subsequently penetrates the vascular or the lymphatic channels adjacent to the tumor. Malignant cells either remain and grow at the sites of penetration or they move on to other tissues, through the circulatory system or in the lymphatics where they arrive at the lymph draining nodes where they proliferate and are transported to adjacent lymph nodes or through the blood stream. The first node to receive drainage from a cancer-containing area of the breast is the "sentinel" node.

Two additional or accessory directions for lymphatic flow from the breast have been described; the transpectoral and the retropectoral routes (Figure 18)[165]:

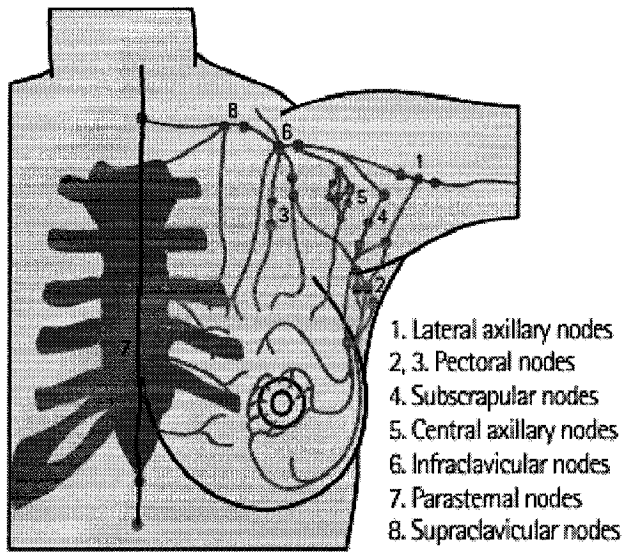


Figure 18. Lymphatic system serving the breast.
Lamarque J-L, ed. Anatomy and embryology. An atlas and text of the breast: Clinical radiodiagnosis. London: Wolfe Medical Publications, 1984: 17-28

1. The transpectoral route includes Rotter's or interpectoral lymph nodes. It begins in the loose areolar tissue of the retromammary plexus and spreads between the pectoral fascia and breast to perforate the pectoralis major muscle and follow the course of the thoracoacromial artery and terminate in the subclavicular node group.

2. The retropectoral route drains the superior and internal aspects of the breast. Lymphatic vessels from this region of the breast join lymphatic vessels from the posterior and lateral surface of the pectoralis major and the pectoralis minor muscles. This is the major lymphatic drainage by way of the external mammary and central axillary nodal groups or Levels I and II respectively.

The internal mammary nodal group is located in the retrosternal interspaces between the costal cartilages approximately 2 to 3 cm within the sternal margin. This group of lymph nodes traverses and runs parallel to the internal mammary vasculature. The internal mammary lymphatic trunks eventually terminate in subclavicular nodal groups. The right internal mammary nodal group enters the right lymphatic duct and the left enters the main thoracic duct.

Lymphatic permeation and obstruction of the inferior and the deep cervical group of nodes of the jugular-subclavian confluence result in the presence of supraclavicular nodes. Detection of supraclavicular node metastasis is an indication of Stage IV disease. Supraclavicular nodes are found beneath the lateral margin of the inferior aspect of the sternocleidomastoid muscle beneath the clavicle.

A cross-communication of connecting dermal lymphatic channels provides lymphatic flow to the contralateral breast and axilla. Internal and external intercostal muscles have extensive lymphatic drainage parallel to the course of the major intercostals blood supply. Infiltrating breast cancer of the lateral breast will thus have direct lymphatic flow towards the axilla while metastatic cells from tumors of the medial breast will flow towards the internal mammary nodal groups. Bi-directional metastases are evident with invasive central or subareolar cancers.

4.1.2 AXILLARY LYMPH NODES

Three groups of lymph vessels drain lymph centrifugally away from the nipple: lateral, medial (pectoral), and inferior (subscapular). The primary lymphatic drainage (75%) is via the outer, lateral vessels to the axillary nodes in the axilla. It consists of 10 to 30 axillary nodes in clusters of 1-6 nodes. The medial (central) vessels lead to seven parasternal or internal mammary nodes followed by eight to the supraclavicular nodes. The inferior vessels reach the infraclavicular nodes and the lymphatic system of the opposite breast.

A different classification (Level I-III) of axillary lymph nodes, commonly used in surgery, is in association with the pectoralis minor. This is described in Figure 19.

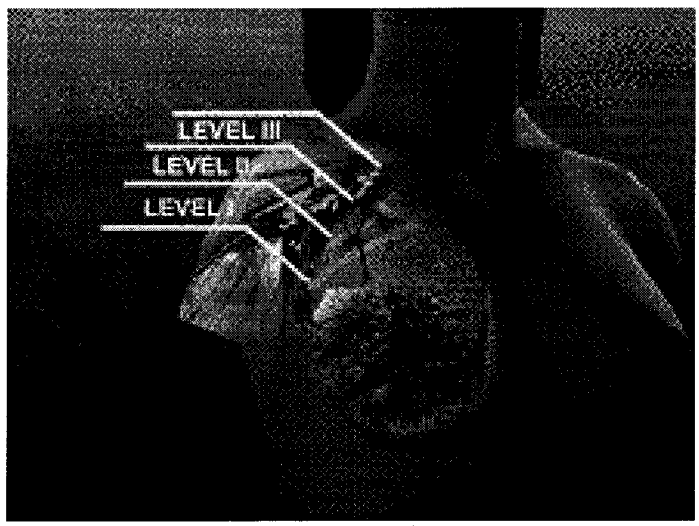


Figure 19. Levels of axillary lymph nodes

1. Level I:

   These lymph nodes are located lateral to or below the lower border of the pectoralis minor. They include the external mammary, axillary vein and scapular lymph node groups.

2. Level II:

   These lymph nodes are located in deep or posterior to the pectoralis minor and they include the central and part of the subclavicular lymph node groups.

3. Level III:

   The last group of lymph nodes is located medial or superior to the upper border of the pectoralis minor. They include the subclavicular lymph node group.

4.1.3 Axillary Lymph Node Dissection

An important component of the physical examination of the breast is the palpation of the axilla for the detection of palpable lymph nodes. This may be an indication of metastasis from a primary breast cancer. Nevertheless, the absence of palpable axillary lymph nodes cannot be considered as an accurate indicator of lymph node metastasis and assessment of the stage of the disease. If breast cancer is present

axillary lymph node metastasis could only be detected by surgical dissection of the nodes and their histological examination.

Axillary lymph node dissection is mainly performed for staging of the disease. Controversy exists as to whether the removal of axillary lymph nodes with metastatic invasion offers only staging information. It is possible that it also provides regional control of disease by reducing the probability of metastasis in the axilla. In a retrospective review of patients that underwent lumpectomy without axillary dissection, 28% recurrence in the axilla over a 10-year period. This recurrence rate varied with tumor size, from 10% for T1a and T1b primary tumors, 26% for T1c tumors, and 33% for T2 to T4 tumors[166]. Data in the literature have shown that in clinically node-negative patients, simple mastectomy without axillary dissection is associated with an axillary recurrence rate of 17.8% to 19.0%[167-171]. On the other hand, when modified radical mastectomy was performed with axillary dissection, the recurrence rates varied from 0.3% to 3.1% for node-positive patients and 1.0% to 2.1% for node-negative patients[167-171]. Data from several studies, including over 3,500 patients that were negative for axillary lymph node metastasis, have shown that the 5-year probability of recurrent cancer in the axillary lymph nodes ranged from 19% when no nodes were removed to 3% when more than 5 or 6 nodes were removed[167-171].

Although the controversy regarding therapeutic benefit of axillary lymph node dissection is not yet resolved, there is strong evidence that the removal of the metastasized nodes reduces the probability of local recurrence of cancer. Traditional axillary lymph node dissection involved removal of more than 15-20 lymph nodes. Recent research has shown that the removal of fewer nodes is adequate to achieve staging and regional control of disease. However, the number of axillary nodes needed to be removed could be reduced even further if the nodes with metastasis could be identified and excised. Given that only the presence of nodal metastasis is important, the removal of relatively more nodes with metastasis and less healthy nodes would improve the control of disease and could reduce morbidity associated with surgery as described in the following section[172-175].

Axillary lymph node dissection is associated with a high risk of both immediate and late post-operative complications, mainly lymphedema and sensory motor disturbances[172-184]. The frequency and severity of post-dissection morbidity varies with the extent of axillary surgery performed[172-184]. Postoperative infection of the breast and axilla has been reported in 5% to 14% of cases[172-175]. Damage to the intercostobrachial nerve causes numbness and dysesthesia in the inner side of the upper arm in almost 80% of patients and restriction of shoulder movement in an estimated 17% of patients undergoing axillary lymph node dissection[172-184].

The most serious and resistant to treatment complication of axillary dissection is lymphedema of the arm ipsilateral to the dissected axilla. The frequency of this complication varies with the extent of the operation from 2% to 27%[172,177-184].

4.2 SENTINEL LYMPH NODE BIOPSY

Recently, in an effort to reduce the complications associated with traditional axillary node dissection, the dissection and assessment of the sentinel node has been evaluated for its accuracy in establishing the metastatic status of the remaining axillary lymph nodes. As defined by Morton and colleagues the sentinel node is the first lymph node on a direct drainage pathway from the primary lesion[185,186]. Sentinel-node biopsy is based on the principle that cells that detach from a primary malignant tumor in the breast will most likely metastasize in the first node that receives lymph from the affected area of the breast[184-189].

Sentinel lymph node biopsy involves the surgical removal of the sentinel node(s). These are marked by a radiopharmaceutical before surgery, and are identified with the use of a gamma-ray tracer, the gamma-probe. A small dose of radiolabeled particles is injected close to the tumor at least 2 hours before surgery. The radioactive tracer migrates through the lymphatic capillaries and reaches the first sentinel lymph node. Both the tumor and the sentinel node can be identified through

scintigraphic images which are obtained 15, 30, 60 and 180 minutes after injection. During surgery, sentinel node biopsy is performed with the aid of a gamma ray detection probe (Figure 20).

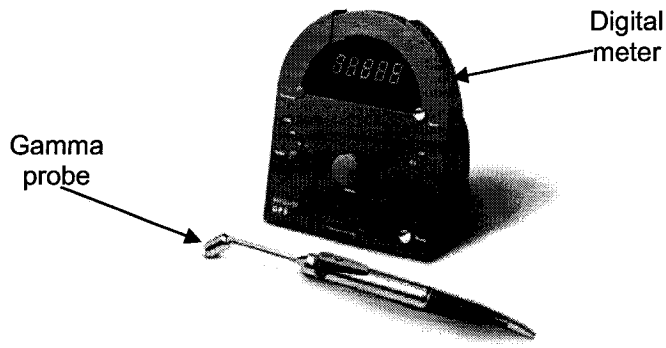


Figure 20. Gamma probe and digital meter

The gamma probe is a small tube capable of detecting the radioactivity emitted from the node that has received the injected radiopharmaceutical, known as the "hot node". The gamma probe transduces the radioactivity signal into acoustic signals and also creates a digital readout. The intensity and frequency of the auditory signal are directly proportional to the radioactivity detected. Aided by the probe, the surgeon is able to locate the lesion and determine the shortest surgical access path to the node.

4.3 CLINICAL PHARMACOLOGY OF RADIOPHARMACEUTICALS

Technetium has become the most widely used radionuclide for diagnostic Nuclear Medicine. It is preferred due to its short half-life, low

energy of its mono-energetic gamma ray and its ease of chelation, which facilitates its incorporation into a wide range of radiopharmaceuticals. It is formed from the decay of the parent radionuclide, molybdenum-99.

When lymphatic mapping is performed with a radiolabelled colloid, the choice of radiocolloid is important because the distribution depends on particle size. The ideal radiocolloid particle size is reported to be between 10-200nm[190-193]. Commonly used radiocolloids in Europe and North America are ^{99m}Technetium Colloidal Albumin and ^{99m}Technetium Sulphur Colloid. Success rates reported for identifying sentinel node with radiocolloid alone are between 88–99%[190,191]. Particle size of these radiocolloids are: colloidal albumin (less than 80 nm) and 200–1000 nm (Albu-Res, Sorin Biomedica Diagnosis, Saluggia, Italy)) and sulphur colloid (200–1000 nm)[192-193].

^{99m}Technetium Sestamibi is a cationic ^{99m}Technetium complex. The accumulation of ^{99m}Technetium Sestamibi in tumours is likely related to a number of variables. ^{99m}Technetium Sestamibi is a lipophilic monovalent cation (an isonitrile compound). It enters the cell via passive diffusion across plasma and mitochondrial membranes. It is postulated that ^{99m}Technetium Sestamibi accumulates within the mitochondria and cytoplasm of cells on the basis of electrical potentials generated across the membrane bilayers. At equilibrium it is sequestered largely within mitochondria by a large negative transmembrane potential. The agent is fixed intracellularly as long as cell membrane integrity is intact and

nutrient blood flow persists[149]. Mitochondria are organelles that supply cells with energy. Complex metabolic changes in malignant cells cause mitochondrial damage which in turn triggers the release of cytochrome-c, and apoptosis and increased membrane permeability.

There are many advantages to using Technetium rather than Thallium for scintigraphic imaging. Technetium's shorter physical half-life permits the use of a higher dose of the radiopharmaceutical. This translates to a higher count rate, which will shorten imaging times and provide sharper pictures. The gamma energy of Technetium (140 KeV) is optimal for use with the detector crystal used in the gamma camera and will undergo less attenuation and scatter. Technetium is also readily available and produced daily from a Molybdenum generator in most Nuclear Medicine departments.

4.4 CANADIAN CLINICAL PRACTICE GUIDELINES FOR BREAST CANCER

Whether axillary lymph node dissection is required for the management of early stage clinically node negative breast cancer is a subject of controversy. Some argue that due to the significant rates of axillary node involvement and due to its potential benefit for control of metastasis in the axilla, an axillary node dissection is indicated for all breast cancer patients[194].

The following are the relevant sections of the Canadian Clinical Practice Guidelines for the management of breast cancer[194]:

a. Removal and pathological examination of axillary lymph nodes should be standard procedure for patients with early, invasive breast cancer.

b. For accurate staging and to reduce the risk of recurrence in the axilla, level I and level II nodes should be removed.

c. Patients should be made fully aware of the frequency and severity of the potential complications of axillary dissection.

d. Increased caution should be practised during radiotherapy of the axilla after axillary dissection.

e. Omission of axillary dissection may be considered when the risk for axillary metastasis is very low or when knowledge of node status will have no influence on therapy.

The Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer was convened by Health Canada in 1997. Since then, evidence has shown that the removal of fewer nodes specifically the metastasized lymph nodes, would offer sufficient staging information and control of local recurrence. Consequently, this would lead to reduced morbidity after axillary dissection.

In 2001, the Steering Committee revised the Guidelines giving the option to patients of having sentinel lymph node biopsy under the

following conditions[195]. Axillary dissection continues to be the standard of care for the surgical staging of operable breast cancer. If a patient opts for SLN biopsy, the benefits and risks as well as what is and is not known about the procedure should be clearly explained to the patient. Specifically, patients should be informed of the number of SLN biopsies performed by their surgeon and the surgeon's success rate with the procedure, as determined by the identification of the SLN and the false-negative rate. Furthermore, the surgeon must perform breast cancer surgery frequently, should become familiar with literature on the topic and the techniques needed to perform the procedure and follow a defined protocol for all 3 aspects of the procedure (nuclear medicine, surgery, pathology). It is also recommended that the first 30 sentinel lymph node biopsies with are followed by complete axillary dissection. Of these 30 cases, at least 10 should have metastatic disease in the axilla. After an 85% success rate in identifying the sentinel lymph node and a 5% or lower false-negative rate the surgeon can perform sentinel lymph node biopsy without full axillary dissection as long as the sentinel lymph node excised is negative for metastasis. A positive sentinel lymph node biopsy result or failure to identify an SLN should be followed by full axillary dissection.

In summary, the Canadian Clinical Practice Guidelines for axillary lymph node dissection in the management of breast cancer continue to recommend the excision of Level I and II nodes. Sentinel lymph node biopsy is offered under strict conditions only if the patient requests it. One

of these conditions recommends a full axillary lymph node dissection if the sentinel lymph node is positive for metastasis. Hence, more healthy axillary lymph nodes will continue to be excised among those with metastasis. This will not help reduce the morbidity associated with axillary lymph node dissection. On the other hand, there remains, depending on the surgeon's success rate, a 6.8% probability of a false negative sentinel lymph node[43,191,198,200,203-207,209,212,215,217,219,221,223,224,227-230,232,235,236,238-243,245,246,248-250]. According to the Guidelines, if the sentinel node is negative for metastasis, no further axillary dissection should be performed, given that the surgeon fulfills the conditions described above. Consequently, in order to minimize the false negative rate, the need for a detection technique specific to metastasized nodes is now higher. This could be made possible by more research aimed towards the validation of a minimally invasive technique that first, will accurately identify lymph nodes with metastatic infiltration and second, will offer proper direction for the surgeon to locate and excise these nodes. The objective of this study is to evaluate the accuracy of lymphoscintigraphy with a malignancy specific radioactive agent to identify axillary lymph nodes with metastasis from a primary breast cancer in a specific area of the ipsilateral breast.

5 SENTINEL LYMPH NODE BIOPSY – LITERATURE REVIEW

A search of the medical literature identified 163 studies related to sentinel lymph node biopsy, of which 104 were excluded. Of these 104 studies, 22 were excluded because they were published in a foreign language, 66 were narrative reviews, 3 were commentaries, 2 were conference proceedings, 2 were repeated publications, 1 was telephone survey and 9 were technical assessments. The remaining 60 studies that were used in this literature review are listed in Appendix 13[43,191,196-198,200-252]. The main conclusions of the literature review are summarized in the following sections.

Axillary dissection used primarily for staging of the axilla for lymph node metastasis in breast carcinoma patients has been associated with substantial morbidity, such as lymphedema, pain, sensory and mobility disturbances of the arm[169,179-181,196-198,256]. Sentinel lymph node dissection, removal of fewer lymph nodes results in reduced risk for this condition[179-181,196-198,256].

Microscopic analysis of fewer sentinel nodes removed could be more elaborate and detailed since the detailed analysis of only one or two sentinel nodes requires a significantly smaller number of sections to be evaluated than that for the larger number of nodes included in a traditional axillary dissection. Newly implemented techniques such as the detailed microscopic analysis with haematoxylin & eosin (H&E) staining,

immunohistochemistry using monoclonal antibodies against cytokeratin and reverse transcriptase-polymerase chain reaction (RT-PCR) have significantly improved the accuracy of micrometastasis detection in the sentinel lymph node. This in turn has increased the accuracy of sentinel lymph node assessment and its ability to accurately represent the metastatic status of the axillary nodes[185,186,189,206].

The most important issue with respect to sentinel lymph node biopsy is whether the metastatic status of the sentinel node could be used to determine the status of the remaining axillary lymph nodes. The relevant efficacy parameter of sentinel lymph node biopsy (SLNB) for the identification of axillary lymph node metastasis is therefore false negative rate. Given that the detection of even one lymph node with malignant infiltration is sufficient for the diagnosis of metastasis, a false positive result is not possible. Therefore a metastasized sentinel node confirms metastasis regardless of the status of the other axillary lymph nodes. Contrary, a false negative sentinel lymph node would lead to the false diagnosis of no axillary lymph node metastasis. According to the Canadian Guidelines, a negative for metastasis sentinel node should not be followed by further axillary dissection[195]. Therefore, the patient will not be staged correctly and will not follow the appropriate adjuvant treatment.

The efficacy of SLNB and the proportion of false negatives was reported in 35 of the 60 studies reviewed, including a total of 15,052 patients and 7,708 sentinel lymph node biopsies[43,191,198,200,203-

[207,209,212,215,217,219,221,223,224,227-230,232,235,236,238-243,245,246,248-250]. In these studies the mean proportion of false negatives was 6.8% (standard deviation 2.8%), ranging from 0% to 46%. The most frequently reported false negative rate was 0% in 6 of the 35 articles (16.7%) involving a total of 339 patients[43,198,204,209,217,235]. In 30 (85.7%) of the 35 studies, the reported false negative results range between 0% and 9%[43,191,198,200,203-206,209,212,215,217,219,221,224,227,228,230,232,235,236]. In general, all authors concluded that sentinel lymph node biopsy is efficacious and may replace traditional axillary lymph node dissection in tumors smaller than 1cm in diameter. The frequency of the false negative rates in published literature between January 1991 and July 2005 is described in Appendix 14.

Of the 7,708 patients who underwent a sentinel lymph node biopsy in these 35 studies, 1,995 (25.8%) had sentinel nodes correctly diagnosed as positive for metastasis. In compliance with the Canadian Clinical Practise Guidelines, all 7,708 of these patients would require full axillary lymph node dissection to determine the extent of metastatic disease. However, with the implementation of sentinel lymph mode biopsy, 5,713 (74.8%) patients could have been spared this invasive procedure. The mean associated risk of missing a metastasis (false negative) was 6.8%.

Three studies evaluated the association between tumor characteristics and axillary lymph node metastasis, and sentinel lymph node dissection efficacy. All authors agreed that, tumor size and lymphovascular invasion are directly related to the risk of metastatic

invasion of the axilla. One study emphasized the reverse correlation between body mass index (BMI) and sentinel lymph node accuracy. However the other two authors contributed the increased failure rate to a decreasing radioactive node count with increasing age and BMI. However, with surgeon awareness and caution, along with the combination of vital blue dye, increased age and BMI did not significantly affect the failure rate for accurate sentinel lymph node localization. Successful sentinel node detection was independent of tumor location and history of breast surgery[211,251,252].

The data reported in 20 studies suggest that while vital blue dye and radiocolloid mapping were effective, the combination of both was more sensitive than either method alone [43,191,198,200,203,204,206,212,219,221,224,228-230,239,245,246,248-250].

In conclusion, the review of the literature on sentinel lymph node biopsy published between January 1991 and July 2005 has shown advantages of sentinel lymph node biopsy over traditional axillary lymph node dissection.

The data in the literature have shown that sentinel lymph node biopsy is a less invasive and safer technique in comparison to traditional axillary lymph node dissection. Even though certain post-operative adverse events have been reported after sentinel node biopsy, a significant decrease of reported short and long-term post-operative

morbidity has been observed when compared to traditional axillary lymph node dissection.

Sentinel lymph node biopsy is efficacious for breast cancer staging in patients with tumors smaller than 1cm in diameter. The overall false negative rate was 6.8% (SD 2.8) and ranged from 0% to 46%. Approximately 75% of the patients submitted to sentinel node biopsy were negative for metastasis and could be spared the axillary lymph node surgery. Tumor size and lymphovascular invasion are directly related to the risk of metastatic invasion of the axilla. Successful sentinel node detection was independent of tumor location and history of breast surgery. Even though increased age and BMI are not contraindications to sentinel lymph node biopsy, extra caution is required because the radioactive node counts are lower than in younger patients and patients lower BMI.

6 PURPOSE, MATERIALS AND METHODS

6.1 RATIONALE AND PURPOSE

Increased public awareness for breast cancer has led to an increased number of women attending and routinely complying with a screening program which include mammographic imaging rather than relying on a simple self-examination of the breast, to detect any breast abnormalities. This has led to the detection of an increased number of

non-palpable lesions and consequently to an increased frequency of detection of mammographic findings suspicious for malignancy[253,254].

As a result, the number of minimal or T1 breast cancer diagnosed is also increasing ("Minimal breast cancer" is considered a non-palpable infiltrating malignant tumor of greater diameter less than 10 mm. or a non-infiltrating (in situ) malignant tumor of any size).

Once the diagnosis of breast cancer has been confirmed, the most important predictive factors of 10- and 20-year survival are the histological type of malignancy and the staging of the disease. The two most important requirements of a staging method are: first, the staging methodology must provide an accurate assessment of the extent of disease and second, this assessment must yield accurate prognostic information that can be used to guide therapy.

Breast cancer staging is based primarily on the metastatic status of the axillary lymph nodes. Conventionally, this information is acquired by the histopathological examination of dissected Level I and II axillary lymph nodes. In addition to requiring general anaesthesia, axillary lymph node dissection is associated with significant morbidity, with up to 60% of the patients experiencing post-operative lymphedema of the involved extremity, neuropathy of the arm and the formation of neuroma or seroma[169, 172,177,179-181,196-198,256-260].

The first lymph node or clusters of nodes to be mapped by lymphoscintigraphy, referred to as the sentinel lymph node(s), are the first to receive metastatic invasion if the tumor has metastasized. Thus, lymphoscintigraphy permits the identification of the node(s) most likely to have been infiltrated by metastasis by the specific primary breast cancer.

Sentinel lymph node biopsy is considered a less invasive technique for the staging of breast cancer. Nevertheless, it still requires the dissection of the axilla, which is always accompanied by direct and indirect complications either post-operative or from the general anaesthesia used. Being a less invasive technique though, the complications associated with sentinel lymph node biopsy are reported to be up to 80% lower than conventional axillary lymph node dissection[261-264].

If the presence of lymph node metastasis can be reliably detected by a minimally invasive imaging technique, it may be possible that axillary lymph node dissection could be avoided. Considering the morbidity associated with the surgical invasion of the axilla, the use of a potential minimally invasive staging technology for breast cancer could probably result in a significant decrease of post-operative morbidity and consequent improve patient care and quality of life.

The radiopharmaceutical presently used for the labelling of the sentinel node for conventional sentinel lymph node biopsy is filtered

^{99m}Technetium Sulphur Colloid. This radiopharmaceutical maps the lymphatic pathway and lymph nodes that drain lymph from the specific breast area, regardless of the presence of metastasis. Therefore, the presence of metastasis in the lymph nodes mapped can only be identified if the nodes are dissected and examined histologically.

On the other hand, if the radioactive agent attaches specifically to malignant cells and marks them as "hot nodes" so they can be identified by a scanner, it may allow the detection of metastatic lymph nodes without surgical dissection of the axilla. If a non-invasive technique was implemented that would accurately detect the presence of metastasis in the axilla, it could potentially eliminate the need to axillary dissection overall and consequently the problem of post-operative morbidity.

In order for lymphoscintigraphy with ^{99m}Technetium Sestamibi to be accepted and implemented as a test for staging of breast cancer it is imperative that it is proven to be valid, reproducible with high sensitivity, specificity, positive predictive value and most important a very high negative predictive value. Considering that a false negative result may lead to inadequate treatment of a cancer patient, the false negative rate is the most important parameter to be assessed.

The purpose of the current study was to evaluate the accuracy and the clinical utility of lymphoscintigraphy with ^{99m}Technetium Sestamibi as

a staging procedure for breast cancer. The study was designed to capture a representative sample of the female population diagnosed with early stage primary breast cancer with without any clinical indication of axillary lymph node metastasis.

6.2.1 STUDY OBJECTIVE

The objective of the present study is to assess the accuracy of lymphoscintigraphy with ^{99m}Technetium Sestamibi to detect axillary lymph node metastasis from a primary breast cancer.

6.2.2 STUDY HYPOTHESIS

The hypothesis tested is that ^{99m}Technetium Sestamibi can accurately identify axillary lymph node metastasis by lymphoscintigraphy alone without the need for further surgical dissection.

6.3 STUDY DESIGN:

This was a prospective non-randomized study for which patients were recruited from two Montreal hospitals, the Hôpital du Sacré Cœur de

Montréal and the Hôpital Hôtel Dieu de Montréal, between January 2000 and December 2001.

6.3.1 PATIENTS

The study enrolled female patients diagnosed with primary breast cancer, by either cytology or histology, with non-palpable lymph nodes (no clinical indication of axillary metastasis).

All patients were referred by their treating physician to either of the two hospitals for further investigation of clinical or mammographic findings that were suspicious for breast cancer. All patients underwent either a Fine Needle Aspiration for cytological assessment (FNA-C) of tumor tissue or a tumor biopsy, either incisional (tumor tissue sampling) or excisional (complete tumor excision) for histological examination. Patients for whom the diagnosis of breast cancer was confirmed and who fulfilled the study's inclusion criteria, described below, were eligible for enrolment in the study. The treating physician and the hospital staff, informed the patient about the procedure and any possible adverse events associated with the use of radiopharmaceuticals, prior to enrolment of the patient in the study. They also informed the patient that since, according to study protocol, all patients were submitted to a conventional Level I and II axillary lymph node dissection, there were no personal advantages to be gained by the patients from their participation in the study. Patients who accepted to participate in the study were enrolled.

6.3.2 INCLUSION CRITERIA

The following inclusion criteria were applied:

- Female patient with a diagnosis of primary operable breast cancer confirmed by histology or cytology,
- Scheduled axillary lymph node dissection,
- Axillary lymph nodes negative for metastasis upon physical examination,
- Patients with a history of malignancy, other than breast, must be disease free for >5 years
- The procedure has been explained to the patient and the patient has agreed to participate in the trial and has signed a consent form.

6.3.2.1 Description and Justification of Inclusion Criteria:

Female patient with a confirmed diagnosis of primary operable breast cancer by histology or cytology,

There are three parts in this criterion that merit attention:

a. Confirmed Cancer Diagnosis

Surgical staging of cancer can only be justified if the diagnosis of cancer has been confirmed by a methodology accepted as gold standard. In the case of breast cancer, histological or cytological confirmation of malignancy is obligatory. Given the high morbidity of axillary dissection this would be entirely justified and ethically required.

b. Primary Breast Cancer

The main purpose of sentinel lymph node biopsy is to detect regional metastasis in patients with early breast cancer who have no clinical sign that metastasis has occurred. Hence, patients with recurrent or metastatic cancer would not require sentinel node detection since in their case metastasis is known.

c. Operable Breast Cancer

Inoperable breast cancer i.e. inflammatory is well advanced and metastasis once again is expected. Therefore, the sentinel lymph node biopsy is of no value.

Scheduled for axillary lymph node dissection

It would be unethical to schedule an invasive procedure for a patient only for the purposes of the study. Only patients who have been scheduled already for surgery could be enrolled. This

was also useful from a practical perspective in enrolling patients in the study.

Axillary lymph nodes negative for metastasis upon physical examination

Lymph nodes that can be palpated are easily localized and removed and do not require the guidance of imaging techniques or radiopharmaceuticals.

Patients with a history of malignancy, other than breast, must be disease free for more than 5 years

In order to minimize the probability of detecting a lymph node metastasis from a primary cancer other than breast cancer, patients with a previous diagnosis of cancer other than breast cancer needed to be disease free for at least 5 years in order to participate in the study.

The procedure has been explained to the patient and the patient has agreed to participate in the trial and has signed a consent form.

Every effort was made to communicate to the patient the advantages and disadvantages of sentinel lymph node biopsy and to describe the technique to the patients or the accompanying person if the patient was not capable of understanding or communicating in the same language as the hospital personnel. Only patients who fully understood the

procedure and the study and signed the informed consent form were enrolled.

6.3.3 EXCLUSION CRITERIA:

Patients with any one of the following criteria were not eligible to participate in the study:

- Inoperable breast cancer (peau d'orange, inflammatory cancer, infiltration to the skin or chest wall),
- Clinical suspicion of metastasis in the axillary, infraclavicular or supraclavicular lymph node,
- Distant metastasis,
- Bilateral breast cancer,
- Recurrence of breast cancer,
- Previous ipsilateral axillary lymph node dissection,
- Patient previously treated by chemotherapy, radiotherapy or immunotherapy,
- Nuclear medicine test less than 3 days before scheduled surgery.

6.3.3.1 Description and Justification of Exclusion Criteria:

1. **Inoperable breast cancer (peau d'orange, inflammatory cancer, infiltration to the skin or chest wall),**

   As mentioned above, in section a3, inoperable breast cancer i.e. inflammatory is well advanced and metastasis is expected. Therefore, it forfeits the purpose of sentinel lymph node biopsy.

2. **Clinical suspicion of metastasis in the axillary, infraclavicular or supraclavicular lymph node**

3. **Distant metastasis (metastasis in organs or tissues other than intramammary or axillary lymph nodes)**

4. **Bilateral breast cancer (breast cancer diagnosed in both breasts)**

5. **Recurrence of breast cancer (patients with a history of breast cancer, less than 5 years ago, rediagnosed with breast cancer)**

   The above exclusions b, c, d and e are based on the fact that the main purpose of sentinel lymph node biopsy is to detect regional metastasis in patients with early breast cancer who have no clinical sign that metastasis has occurred. Hence, patients with recurrent or metastatic cancer would not require sentinel node detection since, in their case, metastasis is certain.

6. **Previous ipsilateral axillary lymph node dissection,**

Any surgical procedure, regardless of severity, can be the cause for the development of cicatricial (scar) tissue, which would increase the difficulty of the repeat procedure. When the procedure involves a sensitive area such as the axilla with vital tissues like the axillary nerve and vessels in close proximity, the difficulty and probability of complications increases even more. In these cases, until new techniques are adequately investigated and proven, conventional techniques are considered safer and should be used exclusively.

7. **Patient exposed to preoperative chemotherapy, radiotherapy or immunotherapy,**

- Patient exposed to adjuvant therapy in the past have two reasons not to be eligible for sentinel lymph node biopsy.

- First, the resulting architectural distortion and fibrous tissue formed after radiotherapy increases the difficulty of surgery, as described above in paragraph "f".

- Second, these patients are survivors of metastatic cancer, which increases the probability that the current breast cancer

is not a primary malignancy, which as explained in the first inclusion criterion, is one of the basic prerequisites for a patient to be eligible for sentinel lymph node biopsy.

8. **A nuclear medicine test performed less than 3 days before scheduled surgery**

   If a nuclear medicine test was performed 3 days or less prior to the lymphoscintigraphy, the radiopharmaceutical used for the first test may not have washed out and may interfere with the radiopharmaceutical used for lymphoscintigraphy.

6.3.4 STUDY PROCEDURES

The following diagram describes the study procedures.

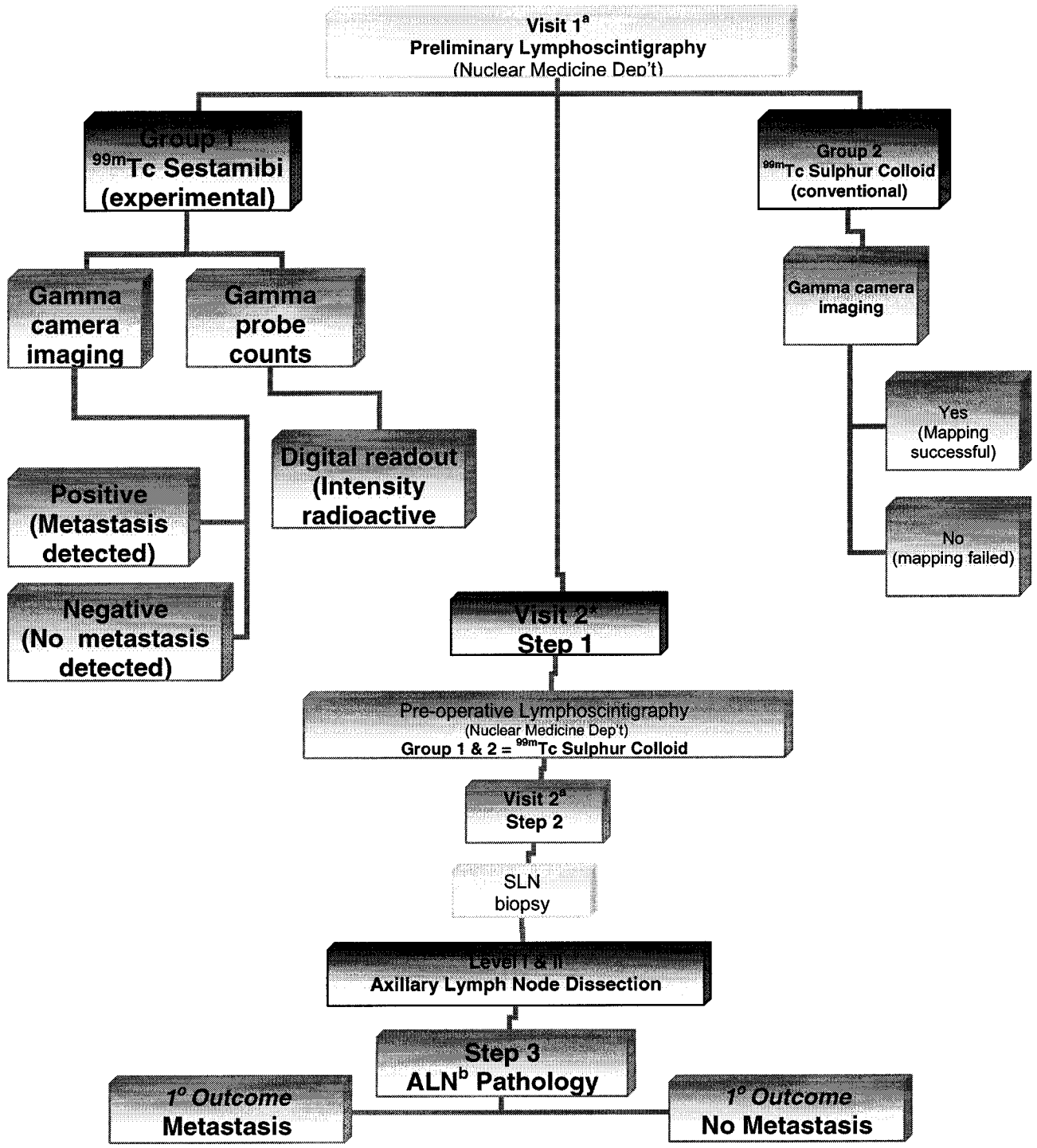


Figure 21: Study Procedures

Upon enrolment it was explained to the patients that they will need to undergo two lymphoscintigraphy tests. One will be done at least one week before the surgery and the other at least 2 hours and not longer than the night before the surgery. The first (preliminary) lymphoscintigraphy was performed to verify if lymphatic drainage from the specific area of the breast where the tumor is located can be mapped. The second (preoperative) was done in order to map the sentinel lymph node(s) and guide the surgeon during surgery.

For the preliminary lymphoscintigraphy, patients were presented with a choice between two radiopharmaceuticals; the conventional ^{99m}Technetium Sulphur Colloid or ^{99m}Technetium Sestamibi. ^{99m}Technetium Sestamibi has not been previously tested for lymphoscintigraphic mapping. In order to avoid jeopardizing the identification and dissection of the sentinel lymph node during surgery the second lymphoscintigraphy was always performed with the conventional ^{99m}Technetium Sulphur Colloid since Sestamibi.

Patients' choice was mainly based on whether they were willing to try a method still under investigation or they would prefer a validated and conventional method instead. All patients were informed that both radioactive agents have been used for different indications and proven to be safe. Depending on their choice, patients were enrolled in one of the two groups described below:

Group 1: Preliminary lymphoscintigraphy with 1,000 MicroCi of ^{99m}Technetium Sestamibi

Preoperative lymphoscintigraphy with 425 – 495 MicroCi of ^{99m}Technetium Filtered Sulphur Colloid

Group 2: Preliminary lymphoscintigraphy with 425 – 495 MicroCi of ^{99m}Technetium Filtered Sulphur Colloid

Preoperative lymphoscintigraphy with 425 – 495 MicroCi of ^{99m}Technetium Filtered Sulphur Colloid

6.3.4.1 Visit 1: Preliminary Lymphoscintigraphy

The same injection technique was followed with both agents. The radiopharmaceuticals were diluted in 6 cc of natural saline and injected in six 1 cc aliquots in separate sites subdermally at the periphery of the breast lesion or at the site of the previous excisional biopsy, if the tumor has been previously removed, followed by injections of 0.2 ml saline. The patient was asked to massage the area of injection mildly in a circular motion.

The areas of the axilla that accumulated radioactivity from the radiopharmaceutical, referred to as the "hot nodes" were identified by two methods. First by gamma-camera imaging with planar scans of the involved breast and axillary area, both anterior and 30° oblique projections, were acquired at 5, 15 and 30 min. and at 2 and 3 hours

after the injection of the radioactive agent. Second, with the use of the digital readout of the gamma-probe counts that measures the intensity of radioactivity in the hot node. All outcomes were recorded and the skin above the first lymph node to be labelled was marked, for reference at the day of surgery.

6.3.4.2 Visit 2, Step 1: Pre-Operative Lymphoscintigraphy

Pre-operative lymphoscintigraphy followed 1 to 3 weeks after the preliminary testing. This time, all patients were tested with ^{99m}Technetium Sulphur Colloid. Between 3 and 24 hours later, the patient was taken to surgery for sentinel lymph node biopsy and axillary lymph node dissection. Before and during surgery the probe was used to guide the surgeon to the location of the highest radioactivity which should represent the sentinel lymph node. The activity level of the node was recorded before dissection (in vivo) as well as after dissection (ex vivo) by a 10-second count. The nodes that had ex vivo radioactive counts of at least 10% that of the hottest lymph node in vivo were considered to be sentinel lymph nodes.

Once the sentinel lymph node was identified and dissected, the surgeon proceeded to the dissection of Level I and II axillary lymph nodes. All removed lymph nodes were sent to pathology for histological analysis. Frozen sections of the sentinel node were performed when possible.

6.3.5 DATA SOURCES, STORING AND ANALYSIS:

Data were abstracted from patient charts at the Hôpital du Sacré Cœur de Montréal and Hôpital Hôtel Dieu by the primary investigator (Fotini Sampalis) and entered in an individual case report form for each patient. The data was then entered and stored in Excel spreadsheets. Data analysis was performed with SPSS.11.0 for Windows.

6.3.6 STUDY VARIABLES:

The variables used in this study and the source of the data are described in the following section. These variables are included in the study "Case Report Form" included in Appendix 15.

The data abstracted were the basic patient demographic information, past medical history, mammographic report, the original histology report confirming breast cancer, and the histology report of the sentinel and axillary lymph nodes excised, details regarding the supplementary surgical treatment and/or adjuvant therapy suggested by the oncology board and follow-up for the duration of the study.

The following data were abstracted each patient's chart:

6.3.6.1 PATIENT'S CHART

a. Basic demographics

   i. Medical Record Number (MRN)

   ii. Date Of Birth

   iii. Ethnic Background

b. Medical history unrelated to breast disease

c. Medical history related to breast disease

d. Latest mammographic report for the breast lesion under investigation

   i. Type of lesion (microcalcifications, soft tissue nodule, combination of both)

   ii. Location (quadrant)

e. The initial cytology or pathology report used for the validation of breast cancer

6.3.6.2 NUCLEAR MEDICINE REPORT

Lymphoscintigraphy (preliminary and pre-operative)

   i. Date of procedure

   ii. Type of radiopharmaceutical used

   iii. Amount of radiopharmaceutical used

   iv. Time between the injection of the radiopharmaceutical

and lymphoscintigraphic imaging on gamma-camera

v. Gamma-camera imaging results (whether or not lymphoscintigraphy mapped the lymphatic drainage from the area of the breast where the primary malignancy was located)

vi. The number of gamma-probe counts per 10 seconds

6.3.6.3 SENTINEL LYMPH NODE BIOPSY SURGICAL REPORT

a. Date of surgery

b. Time interval between the first lymphoscintigram and the biopsy

c. Time interval between the second radiopharmaceutical injection and the biopsy

d. Peri-operative gamma probe counts per 10 seconds

6.3.6.4 PATHOLOGY REPORT

a. Tumor Details

i. Histological type

ii. Grade

iii. Size

b. Sentinel Lymph Node Details

i. Positive or negative for metastatic infiltration

ii. Number of additional sentinel nodes excised

c. Axillary Lymph Nodes excised

i. Positive vs. negative for metastatic infiltration

ii. Number of axillary nodes excised

6.3.7 OUTCOME MEASURES

6.3.7.1 PRIMARY OUTCOME:

The primary outcome was the presence of metastasis in the axillary lymph nodes which was diagnosed by histopathological assessment. The aim of the study was to evaluate the accuracy of ^{99m}Technetium Sestamibi to detect the presence of metastasis in axillary lymph nodes.

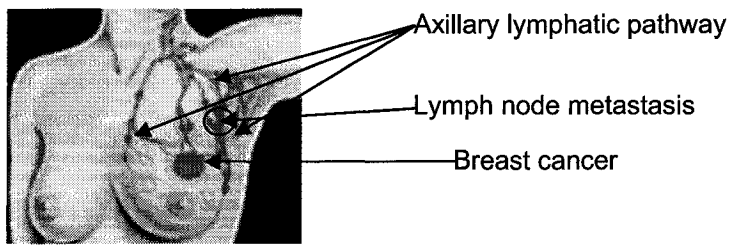


Figure 22. Axillary lymph node metastasis

Detection of metastasis was measured with two methods. The first was an imaging technique with the use of scintigraphic scans obtained with a conventional gamma-camera. The second method was a digital measure of the gamma -probe counts which represent the intensity of radioactivity

in the hot node (Figure 23). The γ-probe used was the Navigator Guidance System 511 KeV with a scintillation crystal that provides high sensitivity for the detection of radioactively labelled cells.

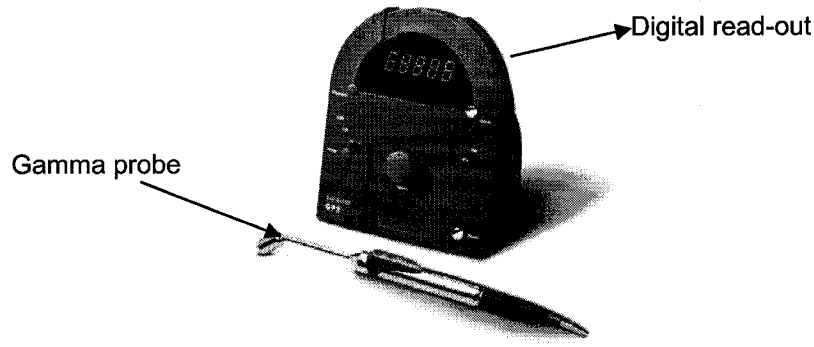


Figure 23.Gamma probe and digital readout

6.3.8 METHODS TO ADDRESS STUDY OBJECTIVE:

Objective 1: To assess the accuracy of ^{99m}Technetium Sestamibi lymphoscintigraphy in identifying axillary lymph node metastasis in patients with confirmed breast cancer

The hypothesis tested is that ^{99m}Technetium Sestamibi lymphoscintigraphy can accurately detect axillary lymph node metastasis in patients with confirmed primary breast cancer.

The accuracy of ^{99m}Technetium Sestamibi to identify axillary lymph node metastasis is based on the comparison between the preliminary lymphoscintigraphy results, both imaging and digital counts, and the histological evaluation of the axillary lymph nodes excised. The unit for

the statistical analysis was the patient and not the number of lymph nodes excised since the outcome of interest is the detection of metastasis and not the absolute number of lymph nodes tested.

For the evaluation of the accuracy of lymphoscintigraphy with ^{99m}Technetium Sestamibi to detect axillary lymph node metastasis the following pairs of observations are possible:

Detection Method		Axillary Lymph Node Metastasis	
		+	-
^{99m}Tm Sestamibi Lymphoscintigraphy	+	(Accurate) (#1)	(Error) (#2)
	–		- (Accurate) (#4)

Table 14: Evaluation of Lymphoscintigraphy with 99mTc Sestamibi results

1. ***Sestamibi has detected metastasis and metastasis is confirmed in at least one of the axillary lymph nodes dissected (#1).***

   Sestamibi correctly detected metastasis; the result is true positive.

2. ***Sestamibi has detected metastasis but no metastasis is confirmed in any of the axillary lymph nodes dissected (#2).***

   Sestamibi falsely identified a metastasis; the result is false positive.

3. ***Sestamibi has not detected metastasis but metastasis is confirmed in at least one of the axillary lymph nodes dissected (#3).***

   Sestamibi failed to detect axillary lymph node metastasis; the result is false negative.

4. ***Sestamibi has not detected metastasis and no metastasis is confirmed in any of the axillary lymph nodes dissected (#4).***

   Sestamibi accurately did not detect axillary lymph node metastasis; the result is true negative.

The association between the gamma probe counts and presence of axillary node metastatis was evaluated with simple logistic regression. In this analysis the dependent variable was the presence of metastasis (0 = No, 1 = Yes) and the independent variable was the gamma probe counts entered as a continuous scale variable.. If a significant association was found a receiver-operating curve was used, to identify the cut-off values for the number of counts that best discriminate between the presence and absence of metastatsis.

Although the objective of the study was aimed at asesing lymphoscintigraphy with Setamibi thet two groups described above were compared for baseline and testing parameters including delay to testing and pathology. These comparisons were conducted in order to determine

whether the patients that agreed to have lymphoscinitgraphy with Seatamibi were comparable to those not agreeing to this procedure. This would allow the assessment of the likelihood of selection bias in the study.

6.4 RESULTS

6.4.1 PATIENT DEMOGRAPHICS

One hundred and ten women with a mean age of 57 (SD = 9.9) years, ranging between 31 and 69 years diagnosed with a primary malignant breast tumor without palpable lymph nodes were enrolled in the study. The patient age distribution is shown in Figure 24.

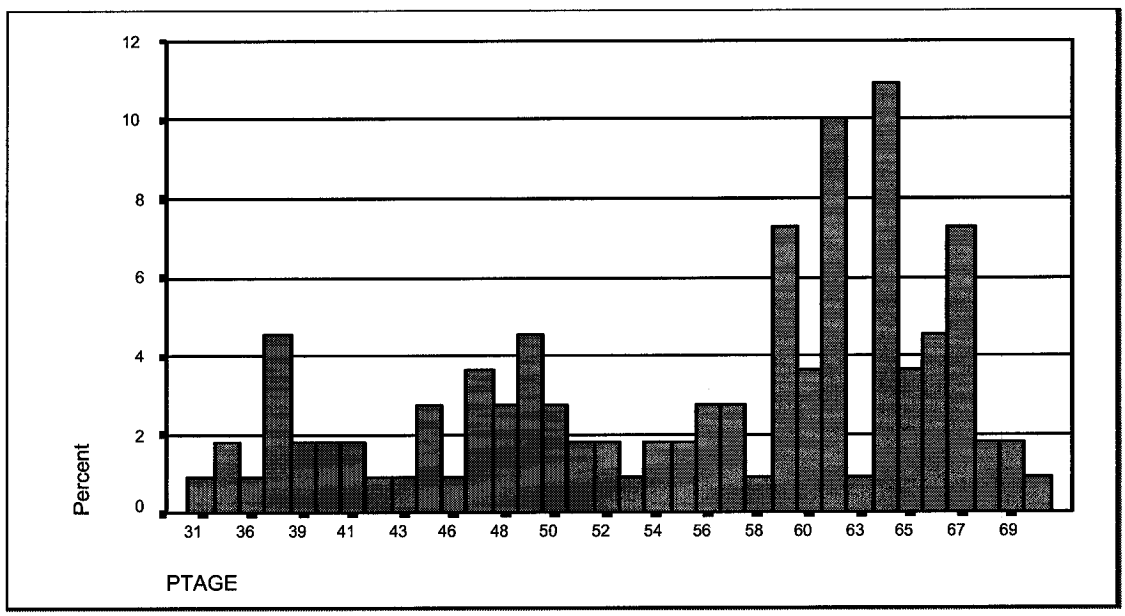


Figure 24: SLN patient age distribution

Of the 110 participating patients 47 (42.7%) patients were enrolled in Group 1 (preliminary lymphoscintigraphy with ^{99m}Technetium

Sestamibi) and 63 (52.3%) patients in Group 2 (preliminary lymphoscintigraphy with ^{99m}Technetium Sulphur Colloid). The youngest patient in Group 1 was 31 years old and the eldest 69 with a mean (SD) age of 55 years (10.1). The age of the 63 patients who were enrolled in the second group ranged between 35 and 70 years, with a mean (SD) age of 56 (9.8) years.

The patients in the two groups were compared with respect to age, time between injection of the radiopharmaceutical and gamma-camera imaging and the time interval between their first and second lymphoscintigraphy. Similarity of age between the different groups of patients tested is important considering that there is a significant association between the risk for breast cancer and patients' age. Student's t-test analysis showed no statistically significant difference for age between the two groups (p=0.588).

Taking into account that the half life of ^{99m}Technetium is 6.5 hours and that the radiopharmaceutical clears or washes out of the cells at different rates, it is important to maintain the same delay between the times of injection and imaging between the two groups in order to ensure similar imaging conditions. All women were submitted to lymphoscintigraphic imaging 5 minutes to 7 hours after the first injection. The mean (SD) delay was 57.4 (64.6) minutes. Standard consecutive gamma camera images were taken at 15, 30, 60 and 180 minutes after the radiopharmaceutical injection. For two (4.3%) patients in the first

group and 2 (6.3%) in the second group the last imaging was delayed for over 3 hours (300 & 420 minutes). These 4 patients were excluded from the analysis of mean imaging delay. The mean (SD) time interval between the second injection and peri-operative detection of the sentinel lymph node was 3.0 (3.24) hours with a range between 30 minutes and 24 hours. The delay for the majority (89%) of the patients was between 2.52 and 3.75 hours.

Given that the risk of metastasis from a primary cancer increases with time, it is important that the time interval between the preliminary and preoperative lymphoscintigraphy is similar between the two groups. For all the patients enrolled in both groups, this time interval ranged from 2 to 227 days, with a mean (SD) delay of 15.7 (27.6) days (95% CI: 10.4, 20.9). The 227 day delay was due to personal reasons of the patient and was excluded from the comparison of mean time interval between tests. For 104 (94.5%) patients, the time interval between the preliminary lymphoscintigraphy and surgery ranged between 2 and 35 days, with a mean (SD) time interval of 10.5 (7.5) days (95% CI 9.1, 12.0). No statistically significant difference was found between the two groups with respect to the time interval between the preliminary lymphoscintigraphy and surgery (p=0.270). The mean (SD) time interval was 14 (7) days (95% CI 4.8, 24.6) after Sestamibi and 23 (6) days (95% CI 10.7, 22.1) after Sulphur Colloid.

The results described above show that the patients included in the study were not different with respect to demographics and test parameters. This would suggest a low likelihood of selection bias.

6.4.2 GENERAL TUMOR CHARACTERISTICS

Among the malignant tumors there were 10 ductal cell carcinomas in-situ (DCIS), 92 infiltrating ductal carcinomas, and 8 lobular infiltrating carcinomas. The distribution of malignant tumors in Group 1 was 5 DCIS, 45 infiltrating ductal carcinomas and 3 lobular infiltrating carcinomas. In Group 2 there were 5 DCIS, 47 infiltrating ductal carcinomas and 5 lobular infiltrating carcinomas. The size of the tumors in Group 1 ranged from 5.1 to 75.3 mm, with a mean (SD) size of 20.8mm (15.1). In Group 2 the tumor size ranged from 4.3mm to 69.8mm. The tumors were almost evenly distributed between the left and the right breast with a slight predominance of the left (54.5% vs. 41.8% respectively). Of the left breast tumors the majority (20%) were located in the left upper inner quadrant followed by the left lower and upper outer quadrants with an equal distribution of 11% each. In the right breast 21% of the tumors were located in the right upper outer quadrant followed by 10% in the right upper central quadrant. The tumor location was similar between the two Groups.

6.4.3 PRELIMINARY LYMPHOSCINTIGRAPHY

6.4.3.1 Lymphoscintigraphic Imaging

Of the 47 lymphoscintigraphies with Sestamibi, 10 (23.4%) detected lymph node metastasis in the axilla ipsilateral to the affected breast and 37 were negative.

6.4.3.2 Axillary Lymph Node Pathology

The mean (SD) number of total axillary lymph nodes excised per patient, including the sentinel lymph node and Level I and II nodes, was 12 (5) and ranged from 2 to 34 lymph nodes. Of the total axillary lymph nodes excised, 14 were positive for metastasis and 96 were negative. The mean (SD) number of nodes excised for Group 1 was 13(3)and 12(6) for Group 2.

6.4.3.3 Preliminary Lymphoscintigraphy versus Axillary Lymph Node Pathology

6.4.3.3.1 ^{99m}Tc-Sestamibi Lymphoscintigraphy Imaging

Of the 10 patients with positive for metastasis ^{99m}Technetium Sestamibi lymphoscintigraphies, 6 (60%) were true positive and 4 (40%) were false positive. Of the 37 patients with negative Sestamibi lymphoscintigraphies, 2 patients delayed 170 and 175 days respectively between preliminary lymphoscintigraphy and surgery. Because the

probability that metastasis may have occurred during the 5.8 month delay, the results of the preliminary lymphoscintigraphy were no longer applicable at the time of surgery. For this reason these two patients were excluded from the analysis. Of the remaining 35 patients with negative Sestamibi lymphoscintigraphies, 31 (88.6%) were true negative and 6 (17.1%) were false negative (Tables 15 and 16). The sensitivity and specificity of lymphoscintigraphic imaging with ^{99m}Technetium Sestamibi were 50% and 88.6% respectively. The positive predictive value was 60%, the negative predictive value 83.8% and the accuracy of the technique to detect axillary lymph nodes invaded by metastatic cells was 78.7%.

Sestamibi Imaging	Axillary Lymph Node Metastasis		Total
	Positive	Negative	
Positive	6	4	10
Negative	6	31	37
Total	10	35	35

Table 15: Lymphoscintigraphic imaging results compared to axillary lymph node pathology

True Positive	6/10	60.0%	6
True Negative	31/35	88.6%	31
False Positive	4/10	40.0%	4
False Negative	6/35	**17.1%**	6

Table 16: Lymphoscintigraphic imaging results compared to axillary lymph node pathology

6.4.3.3.2 Gamma-Probe Counts per 10 seconds

Logistic regression showed a statistically significant ($p<0.001$) association between the counts measured every 10 seconds with the gamma probe during ^{99m}Technetium Sestamibi lymphoscintigraphy and axillary lymph node metastasis (Table 17).

Variable	Parameter estimate (B)	S.E.	P-value	Odds Ratio	95.0% CI for Odds Ratio	
					Lower	Upper
Counts /10sec.	0.002	0.001	0.001	1.002	1.001	1.003

Table 17: Logistic regression results for association between gamma probe counts and axillary lymph node metastasis

The Receiver Operating Characteristic (ROC) curve showed 1,350, 1,962, and 3,080 as the three possible cut-off points between positive and negative for metastasis gamma-probe counts per 10 sec detected with ^{99m}Techetium Sestamibi (Figure 25).

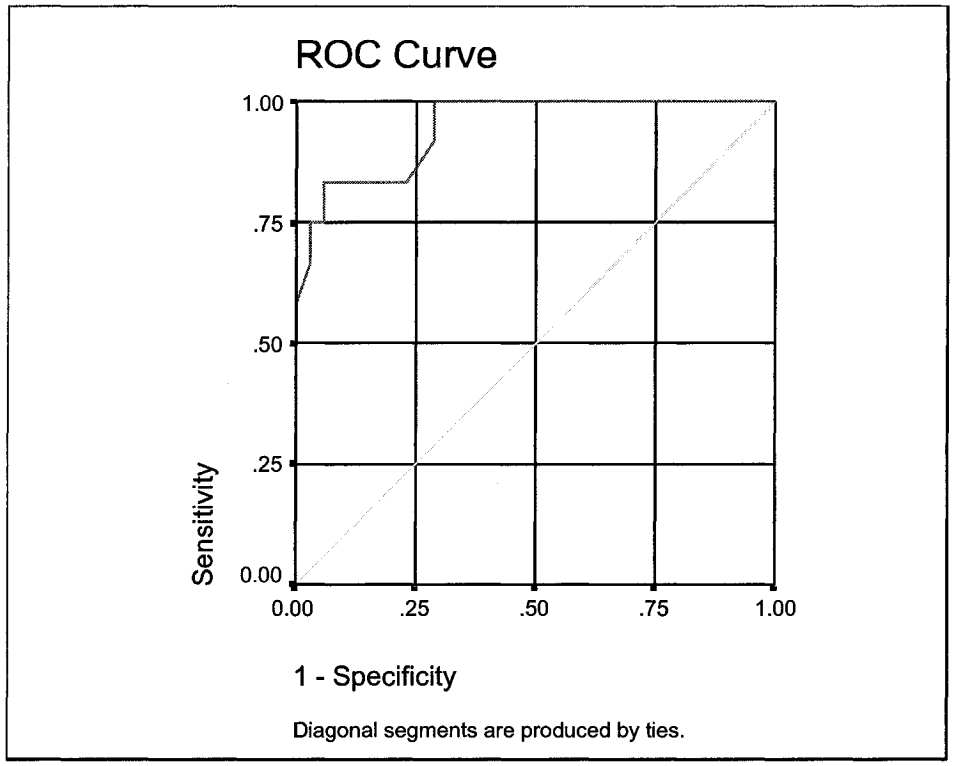


Figure 25: ROC curve of gamma-probe counts versus metastatic status of axilla

At a cut-off at 1,350 counts the sensitivity and specificity of gamma counts would be 100% and 69.7% respectively. The Positive Predictive Value (PPV) would be 54.5%, the Negative Predictive Value (NPV) 100% and the accuracy of the test 77.8%. The proportion of false negatives would be 0%.

With a cut-off of 1,962 counts the sensitivity would be 100% and the specificity 80.0%. The PPV would be 58.8%, the NPV 100.0% and the accuracy 84.4%. There would be no false negative results.

Finally with a cut-off of 3,080 counts the sensitivity and specificity of gamma counts would be 100% and 94.3% respectively. The PPV

would be 83.3%, the NPV 100% and the accuracy of the test 95.6%. There would again be no false negative results (Table 18). Based on these results the cut-off of 3.080 would be selected since it was the one with the highest specificity and positive predictive value.

Gamma counts/10sec.	Axillary Lymph Node Pathology							
1,350 counts	**POS**	**NEG**	**SENS**	**SPEC**	**PPV**	**NPV**	**%FN**	**ACC**
POS	12	10	**100%**	69.7%	54.5%	**100%**	**0%**	77.8%
NEG	0	23						
1,962 counts	**POS**	**NEG**	**SENS**	**SPEC**	**PPV**	**NPV**	**%FN**	**ACC**
POS	10	7	**100%**	80.0%	58.8%	**100%**	**0%**	84.4%
NEG	0	28						
3,080 counts	**POS**	**NEG**	**SENS**	**SPEC**	**PPV**	**NPV**	**%FN**	**ACC**
POS	10	2	**100%**	94.3%	83.3%	**100%**	**0%**	95.6%
NEG	0	33						

Table 18: ROC curve of gamma probe counts vs. axillary lymph node pathology

6.5 DISCUSSION

Once a mammographic abnormality has been confirmed to be malignant, the next step in patient management is to describe the cancer according to its stage and metastasis. This information is required for the decision of the appropriate type of adjuvant therapy. Staging of breast cancer is primarily based on lymph node metastasis of the ipsilateral axilla.

Axillary lymph node dissection is the standard of care for the surgical staging of operable breast cancer. However, axillary dissection is associated with a high risk of both immediate and late post-operative complications, mainly lymphedema and sensory motor disturbances[172-184]. Aiming to reduce the complications of axillary dissection, the Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer of Canada revised the Guidelines giving the option to patients of having sentinel lymph node biopsy under the condition that they are informed about the technique and their surgeon is qualified to practice the procedure[195].

Even though sentinel lymph node biopsy is less invasive than conventional axillary lymph node dissection, it still requires axillary surgery. Surgical invasion of the axilla is associated with a non-negligible risk for complications that is not yet well established because sentinel lymph node biopsy is still regarded as an experimental

procedure. Consequently, in most centers, it is performed concurrently with a further axillary lymph node dissection of level I and II lymph nodes.

According to Guidelines, if metastasis is diagnosed in the sentinel node a full axillary dissection should follow. On the other hand, if the sentinel node is negative for metastasis, no further axillary dissection is recommended, given that the surgeon is qualified.

Considering the above problems, the introduction of a non-invasive technique that is accurate in the detection of metastatic lymph nodes and staging of breast cancer would minimize the need for axillary lymph node dissection, its associated morbidity and reduce the false negative results and the probability of inaccurate staging. The current study evaluated the accuracy and the clinical utility of lymphoscintigraphy with ^{99m}Technetium Sestamibi, a radioactive agent that attaches specifically to malignant cells and marks them as "hot nodes" so they can be identified.

The accuracy of lymphoscintigraphy with ^{99m}Technetium Sestamibi was evaluated with two different methods. The first was the assessment of the gamma-camera image. The sensitivity of ^{99m}Technetium Sestamibi lymphoscintigraphy imaging was 50% the negative predictive value was 83.8% and the proportion of false negative results was 17.1%. Because of the high probability of a false negative result lymphoscintigraphic

imaging with ^{99m}Technetium Sestamibi cannot be considered reliable for the detection of axillary lymph node metastasis.

The second method used in this study was the digital outcome of the gamma probe used to detect and measure the intensity of radioactivity in the hot node. Logistic regression showed a statistically significant ($p<0.001$) association between the gamma probe counts and axillary lymph node metastasis. All three cut-off points identified by ROC analysis had similar sensitivity estimates and false negative rate of 100%. By using the cut-off at 3,080 counts the specificity and positive predictive value were maximum at 94.3% and 83.3% respectively.

The above results suggest that the use of a malignant cell specific radioactive agent for lymphatic mapping combined with the gamma probe digital readout of the intensity of radioactivity in the hot node, may offer an accurate non-invasive procedure for the detection of axillary lymph node metastasis from breast cancer of the ipsilateral breast. Even if these results seem very encouraging, the small number of patients that agreed to be tested with an experimental radioactive agent (Sestamibi) and the even smaller number of patients with axillary lymph node metastasis present a limitation to this analysis. Furthermore, since this methodology has not been previously studied there is no comparative data for the results of the current study.

A limitation of the current is that it is non-randomized and bias may have been introduced first because the women accepting a method being tested for the first time for this indication may differ from women who would reject it and opt for the conventionally used method. On the other hand, selection bias may occur since the surgeon may select the patient most likely to understand and accept experimental versus conventional technology. Comparison of the two patient groups however, would suggest that the likelihood of bias is low.

The strengths of the study are that patients were enrolled in two different centers where the patients were operated by different surgeons and the surgery was not influenced in any way by the type of radioactive agent used in the preliminary lymphoscintigraphy. Furthermore, recording of the gamma probe counts during the preliminary lymphoscintigraphy took place in the nuclear medicine departments of each hospital at least 1 week prior to surgery. The surgeons detecting the sentinel node and performing the biopsy and axillary lymph node dissection were objective since they were blind to the type of radioactive agent used in the preliminary testing. Therefore, no bias could be introduced in the way the surgery was performed between the two groups.

6.6 CONCLUSION:

The current study indicates that the use of ^{99m}Technetium Sestamibi lymphoscintigraphy imaging cannot be considered accurate for the detection of axillary lymph node metastasis.

The results of this study present a strong association between the intensity of radioactivity in the hot node as measured by the gamma-probe counts and the presence of axillary metastasis. These results are encouraging as a first evaluation of this procedure and merit further research. Such research should be performed in centers specialized in the management of breast cancer and among nuclear medicine physicians and surgeons highly experienced in the procedure of sentinel lymph node biopsy.

7 SUMMARY

The purpose of the thesis was to describe and evaluate the effectiveness of two microinvasive procedures for the diagnosis, treatment, and staging of breast cancer.

The first part of the thesis proved that the ABBI offers a superior therapeutic effectiveness, is less invasive, and more cost effective than wire localization excisional biopsy for the management of mammographic abnormalities with high risk for breast cancer. In addition, the ABBI was shown to be safe and well tolerated by most patients. The strong volume-performance association shows that the effectiveness of the ABBI will improve if the surgeons are properly trained.

The second part of the thesis proved that lymphoscintigraphy with ^{99m}Technetium Sestamibi, if practised correctly, offers a highly accurate and non-invasive technique for the detection of axillary lymph node metastasis from primary breast cancer. With proper training and experience, the implementation of lymphoscintigraphy with ^{99m}Technetium Sestamibi can help minimize the morbidity associated with conventional axillary lymph node dissection. Furthermore, it can reduce the probability of missed metastasis observed with the increased practise of sentinel lymph node biopsy for the staging of breast cancer.

In conclusion, the results of this thesis demonstrate that both the ABBI and lymphoscintigraphy with ^{99m}Technetium Sestamibi can help improve the effectiveness of the current management of mammographic abnormalities and specifically breast cancer. Proper training of surgeons on both techniques in highly qualified training centers with a high volume of cases can help improve the practise of these techniques in Canadian hospitals. This may in turn increase the treatment benefits for the patients and reduce the healthcare costs for the management of breast disease and specifically breast cancer in Canada.

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9 APPENDIX

APPENDIX 1: THE TNM STAGING SYSTEM FOR BREAST CANCER

In the TNM system, TNM stands for Tumour, Nodes, and Metastases. Each of these is categorized separately and classified with a number to give the final stage[9].

a. **T** classifies the extent of the primary tumour, and is normally given as T0 through T4. T0 represents a tumour that has not even started to invade the local tissues. This is called "In Situ". T4 on the other hand represents a large primary tumour that has probably invaded other organs by direct extension, and which is usually inoperable.

b. **N** classifies the amount of regional lymph node involvement. It is important to understand that only the lymph nodes draining the area of the primary tumour are considered in this classification. Involvement of distant lymph nodes is considered to be metastatic disease. The definition of just which lymph nodes are regional depends on the type of cancer. N0 means no lymph node involvement while N4 means extensive involvement. In general more extensive involvement means some combination of more nodes involved, greater enlargement of the involved nodes, and more distant (But still regional) node involvement.

c. **M** may be either M0 if there are no distant metastases, or M1 if there are metastases.

APPENDIX 2: TNM CLINICAL CLASSIFICATION

TNM CLINICAL CLASSIFICATION	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ : intraductal or lobular carcinoma
T1	Tumour ≤ 2 cm in greatest diameter
	T1a = Tumour ≤ 0.5 cm in greatest diameter
	T1b = Tumour 0.51 – 0.99 cm in greatest diameter
	T1c = Tumour 1.0 - 2.0 cm in greatest diameter
T2	Tumour 2.1 – 4.99 cm in greatest diameter
T3	Tumour > 5.0 cm in greatest diameter
T4	Tumour of any size with direct extension to the chest wall or skin
T4a	Extension to the chest wall (includes ribs, intercostal muscles and serratus anterior muscle, but not pectoral muscle
T4b	Edema (including peau d'orange) or ulceration of the skin of the breast, or satellite skin nodules confined to the same breast
T4c	Both T4a + T4b
T4d	Inflammatory carcinoma
N - REGIONAL LYMPH NODES	
NX	Regional lymph nodes cannot be assessed (i.e. previously removed
N0	No regional lymph node metastasis
N1	Metastasis to moveable ipsilateral axillary node(s)
N2	Metastasis to ipsilateral axillary node(s) fixed to one another or other structures
N3	Metastasis to ipsilateral internal mammary lymph node(s)
M – DISTANT METASTASIS	
MX	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis including metastasis to supraclavicular lymph nodes

M1 can be further specified according to the following notation:

Pulmonary	PUL	Bone marrow	MAR
Osseous	OSS	Pleura	PLE
Hepatic	PEP	Peritoneum	PER
Brain	BRA	Skin	SKI
Lymph nodes	LYM	Other	OTH

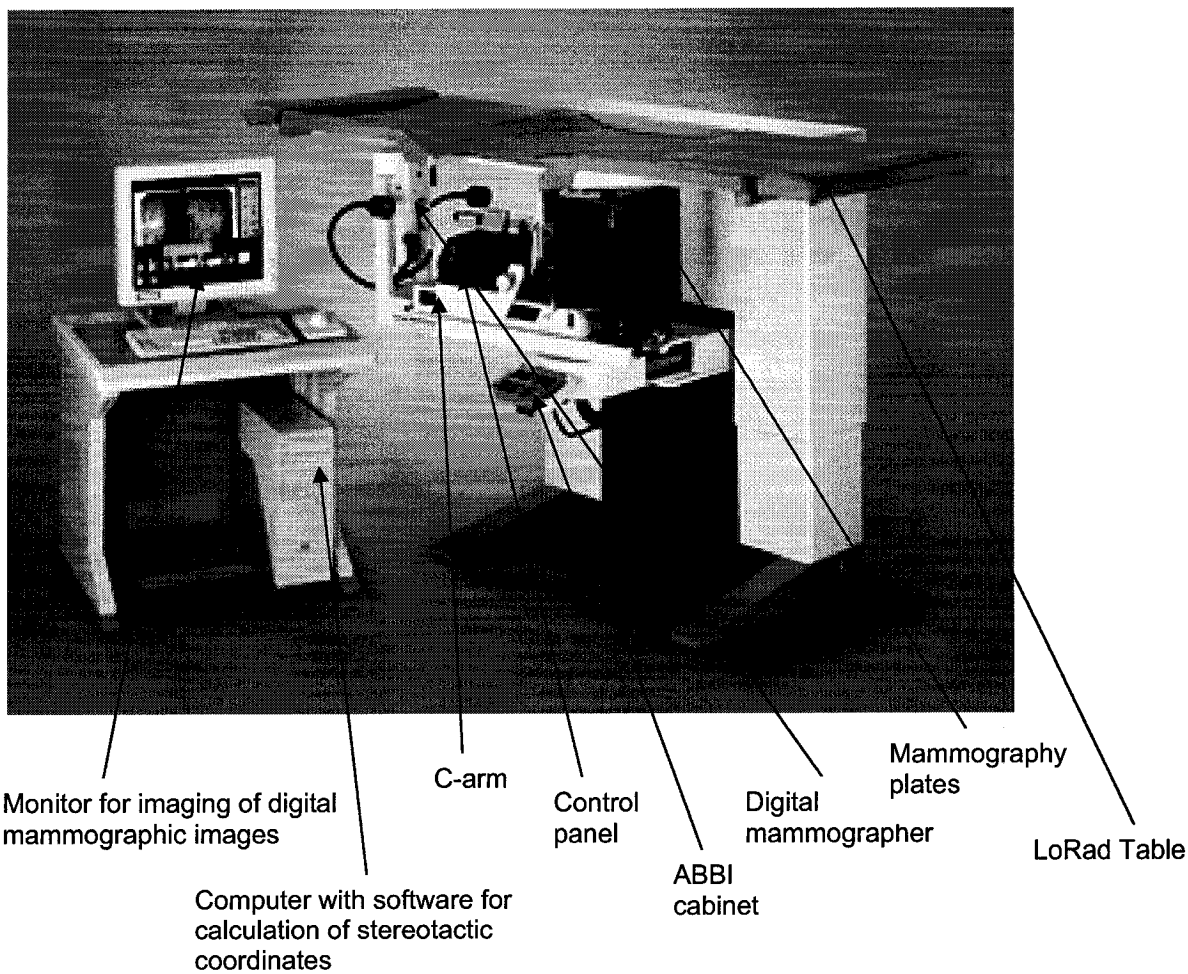
APPENDIX 3: TNM PATHOLOGICAL CLASSIFICATION

pT = Primary Tumour	
The pT categories correspond to the T categories in the clinical classification	
pN = Regional Lymph Nodes	
pNX	Regional lymph nodes cannot be assessed (no axillary lymph node dissection or previously removed)
pN0	No regional Lymph node metastasis
pN1	Metastasis on moveable ipsilateral axillary nodes
	pN1a = only micrometastasis (none < 0.2 cm)
	pN1b = metastasis to lymph node(s), any > 0.2 cm
	pN1bi = metastasis in 1 – 3 lymph nodes, any > 0.2 cm and all < 2.0 cm in greatest diameter
	pN1bii = metastasis to four or more lymph nodes, any > 0.2 cm and all < 2.0 cm in greatest diameter
	pN1biii = extension of tumour beyond the capsule of a lymph node metastasis < 2.0 cm in greatest diameter
	pN1biv= metastasis to a lymph node ≥2.0 cm in greatest diameter
pN2	Metastasis to ipsilateral axillary lymph nodes that are fixed to one another or to other structures
pN3	Metastasis to ipsilateral internal mammary lymph nodes
pM Distant Metastasis	
The pM categories correspond to the M categories in the clinical classification	

Appendix 4: TNM Staging & Classification of Breast Cancer

Stage	Tumour (T)	Classification Node (N)	Metastasis (M)
0	Tis	N0	M0
I	T1	N0	M0
IIA	T0	N1	M0
	T1	N1*	M0
	T2	N0	M0
IIB	T2	N1	M0
	T3	N0	M0
IIIA	T0	N2	M0
	T1	N2	M0
	T2	Na	M0
	T3	N1, N2	M0
IIIB	T4	Any N	M0
	Any T	N3	M0
IV	Any T	Any N	M1

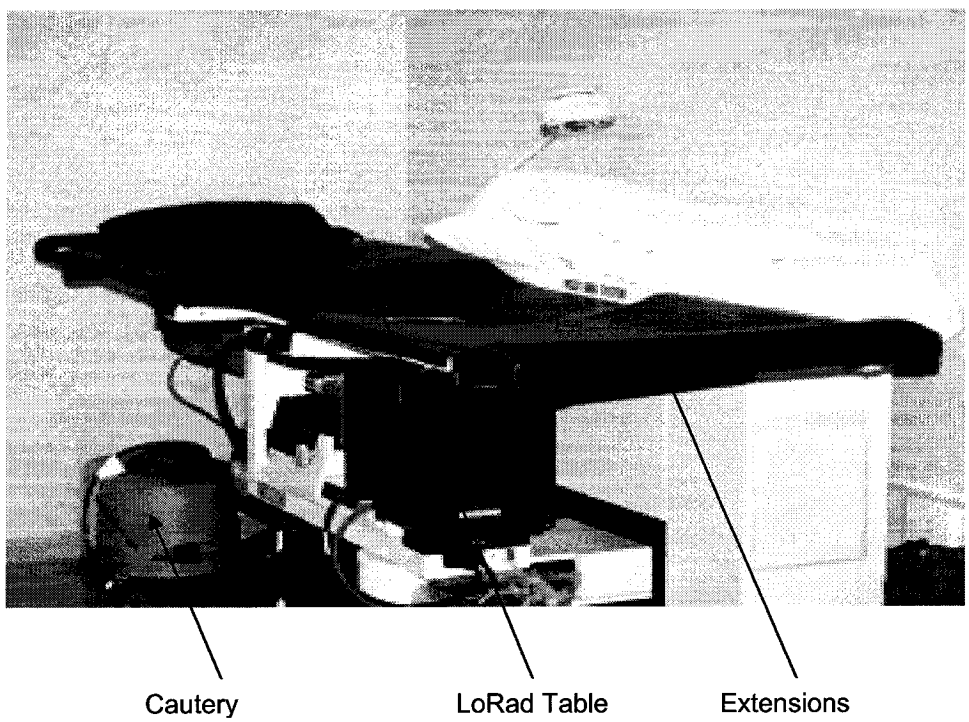
APPENDIX 5: ABBI SURGICAL EQUIPMENT



1. Stereotactic LoRad table

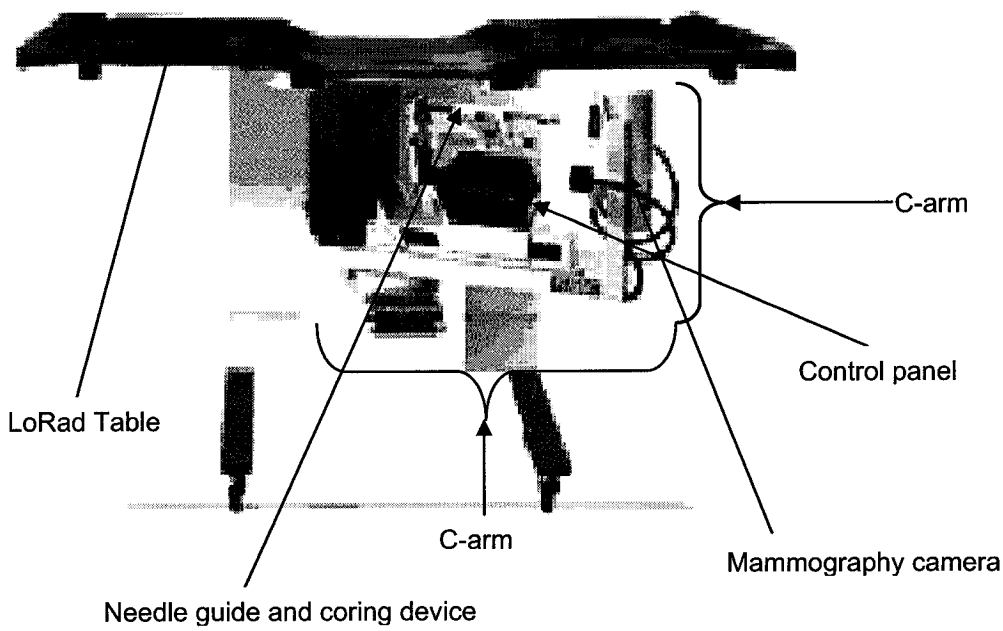
This is an adjustable height operating table with cushioning on top for increased comfort and a circular opening positioned at the upper central part, which allows the woman's breast to hang through. The table is designed to allow 360° access to the area of interest of the breast. The table surface specifications are:

- Height: the table can be moved from 34 inches to 57 inches (86.4cm – 144.8cm)
- Length: 72 inches (182.9cm)
- Width: 28 inches (71.1cm)
- Leg support extensions on either side: 17 inches (43.2cm)



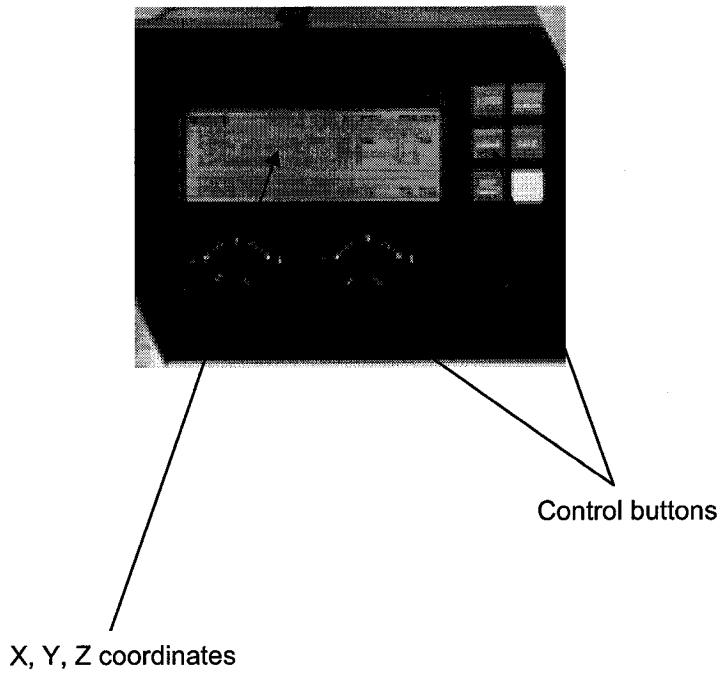
2. C-arm:

The C-arm is a metal base mounted on a pivot mechanism below the surface of the table and can be rotated up to 180^0. It holds the needle guidance stage, a device that aids the insertion of the biopsy needle, which guides the physician during the needle insertion, the coring devise and the components and accessories used to obtain the stereo images. By rotating the devise, it makes it possible to select the best approach for reaching the lesion that will allow a complete excision with the removal of the least possible breast tissue. This may be lateral (outer), medial (inner), or anterior (frontal) to the breast. For example, for a lateral approach the C-arm is turned at 90^0 to the table and the incision is made at the lateral part of the breast.



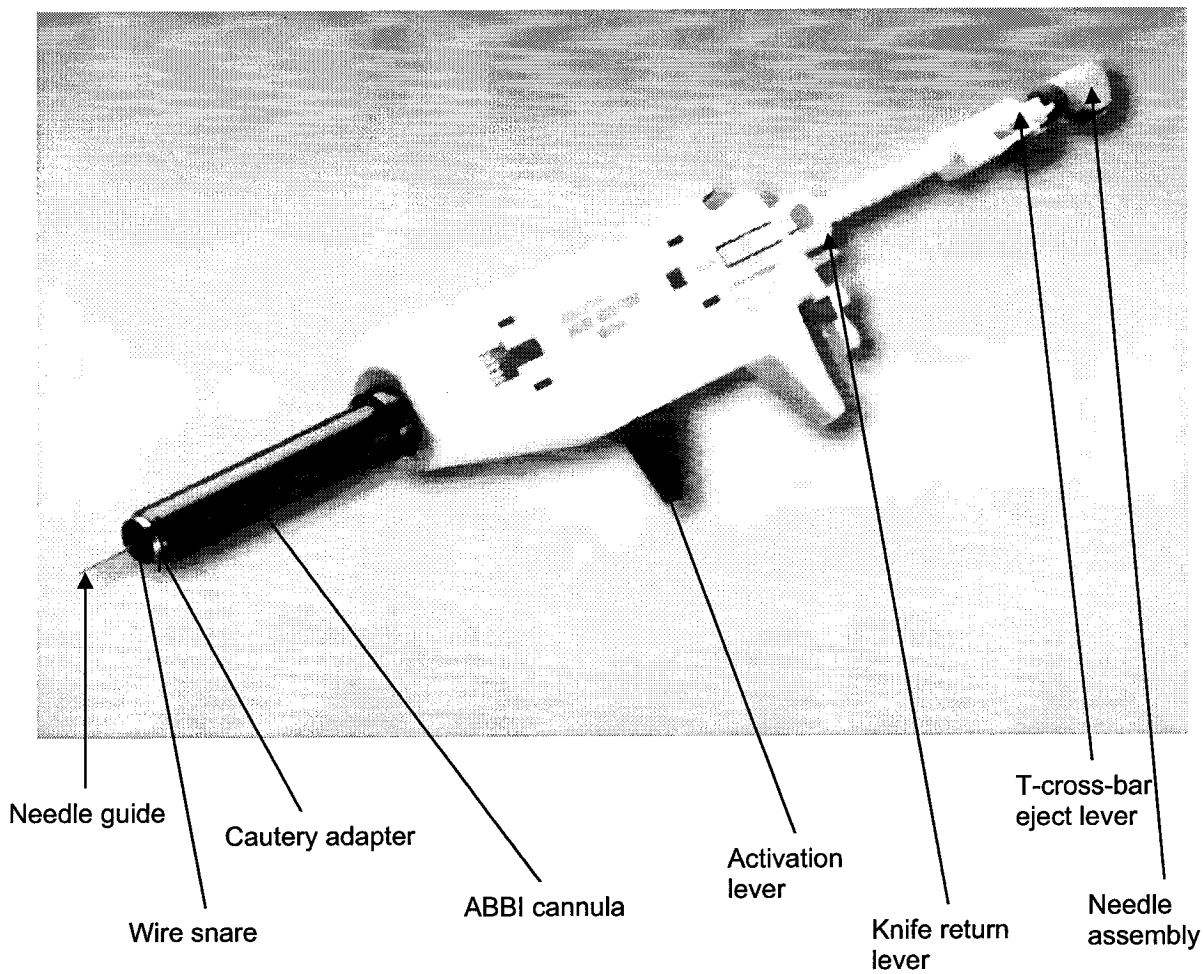
3. ABBI control panel (Fig. 5):

The ABBI panel consists of a numerical and graphical display of the X, Y and Z coordinates which are transferred from the computer. It controls the movement of the coring device in the breast and indicates its proximity to the lesion.



4. ABBI Surgical Component (Fig. 6),

The ABBI surgical component is comprised of a coring device that enters the breast and excises the lesion. The movement of the device in the breast is guided by the stereotactic coordinates obtained from the control panel.



The ABBI surgical component consists of:

4.1. ABBI cannula:

The ABBI cannula is the main part of the coring device. It is cone shaped and made of insulated material that protects the specimen inside the cannula. The cannula also contains a radiolucent sleeve fitted in its interior wall which can slide back and forth in order to allow imaging at any time during the procedure. Perioperative images are done for two reasons; first, to confirm the proper position of the needle guide, that is described in the following section (4.2), and second, to confirm the safety of the posterior margin or the opposite side of the breast, to ensure that the coring device does not penetrate through the breast. The cannula is available in diameters of 5, 10, 15 and 20 mm.

4.2. 16-gauge needle guide:

The needle guide is installed in the center of the coring device. Once the stereotactic coordinates of the lesion have been calculated by the computer (section 1) and transferred to the ABBI control panel (section 3), the needle is quickly inserted in the breast, ideally in the center of the target lesion. The coordinates in the ABBI control panel guide the position of the needle in the breast.

4.3. T-crossbar:

The T-crossbar is a T-shaped sharp edged metal, which is inserted along with the needle in the target area of the lesion. Once the position of the needle is confirmed to be satisfactory, the T-crossbar is ejected into the target. The T shape of the crossbar attaches into the target and stabilizes the needle into the lesion.

4.4. Circular Knife Blade or Wire Snare:

A circular knife blade is located at the edge of the ABBI cannula. This is used to cut the distal end of the specimen. At the same time, cautery is applied at the exterior wall of the cannula for haemostasis of the surrounding breast tissue.

4.5. Activation Lever:

The activation lever is placed at the center of the device. It consists of a handle, which controls the movement of the circular knife blade. Once the cannula has been inserted in the breast and its position is confirmed, the activation lever is pushed to the right in order to activate the blade to cut the distal end of the specimen.

4.6. Cautery Adapter:

The cautery adapter is at the upper part of the device. It consists of a 1 cm metal adaptor, which receives one end of the cord that connects the cautery device with the ABBI cannula. The electrical current is transferred from the cautery device through the

cord to the adaptor, which in turn provides cautery while the wire snare closes simultaneously to transect the distal portion of the breast specimen.

4.7. Knife Return Lever:

The knife return lever is positioned at the lower part of the device and consists of two small handles on either side of the device. This lever has two functions. When the handles are pushed in, it allows a circular ring surrounding the needle assembly to move back and forth so that it can be accurately positioned at the distance of the Z-axis, which refers to the distance the needle will move in the breast in order to reach the target. Once the ring is positioned the handles are released. From this point after, the distance the needle can enter in the breast is locked and secured so that it cannot move further than the manually predefined depth.

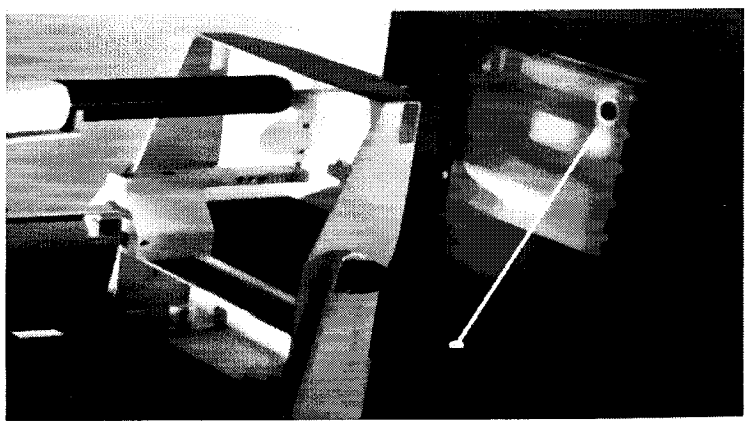
4.8. Needle Assembly:

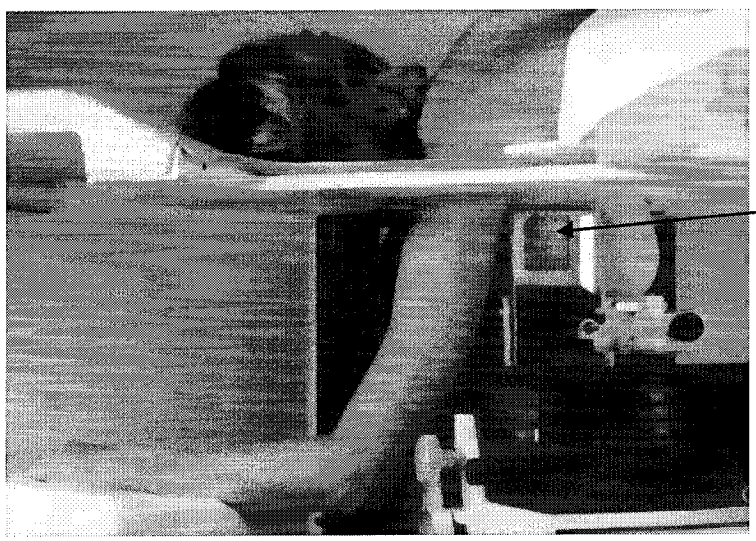
The needle assembly contains the needle and the T-cross bar. At the exterior of the assembly is a ring. By turning this ring, it releases the specimen to be removed from the cannula along with the t-cross bar.

5. Operating Window

The operating window is a 5 X 5 cm square opening at the upper part of a perpendicular 17 X 15 cm metal plate. The breast is

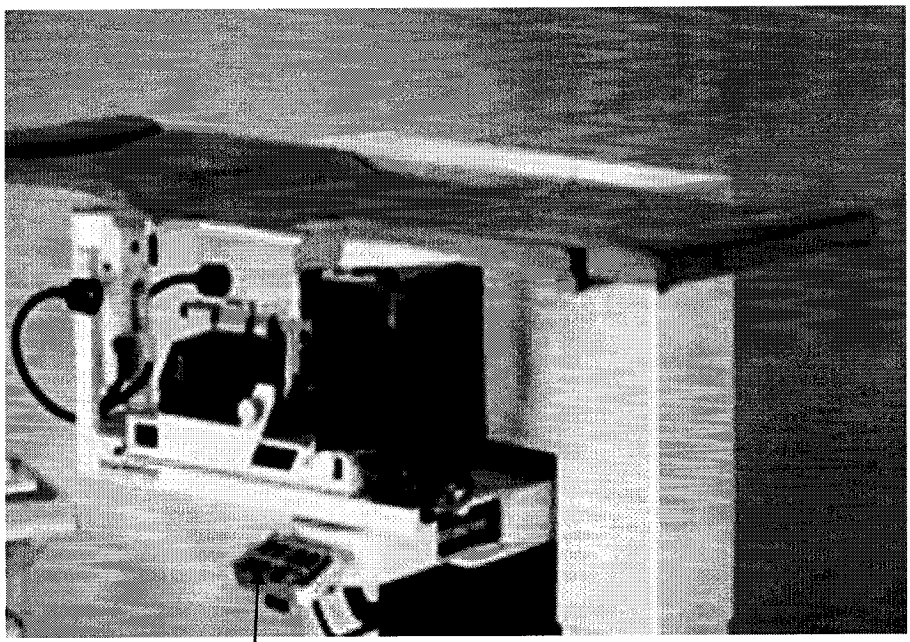
compressed between this metal plate and the imaging receptor. The target lesion is positioned as close to the center of the operating window as possible. The surgery is performed through the operating window.





6. The ABBI Cabinet:

The ABBI cabinet houses the components or levers that drive the C-arm and the Table.



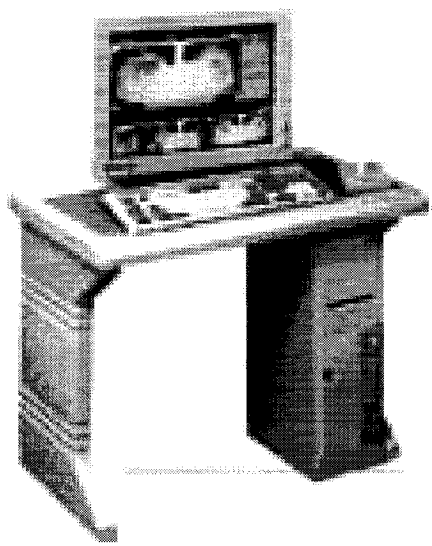
7. Digital Image Receptor:

The digital mammography system converts X-rays into an electronic signal. The mammographic image is portrayed in the ABBI System Operator Workstation.

8. ABBI Operator Workstation (Fig. 10):

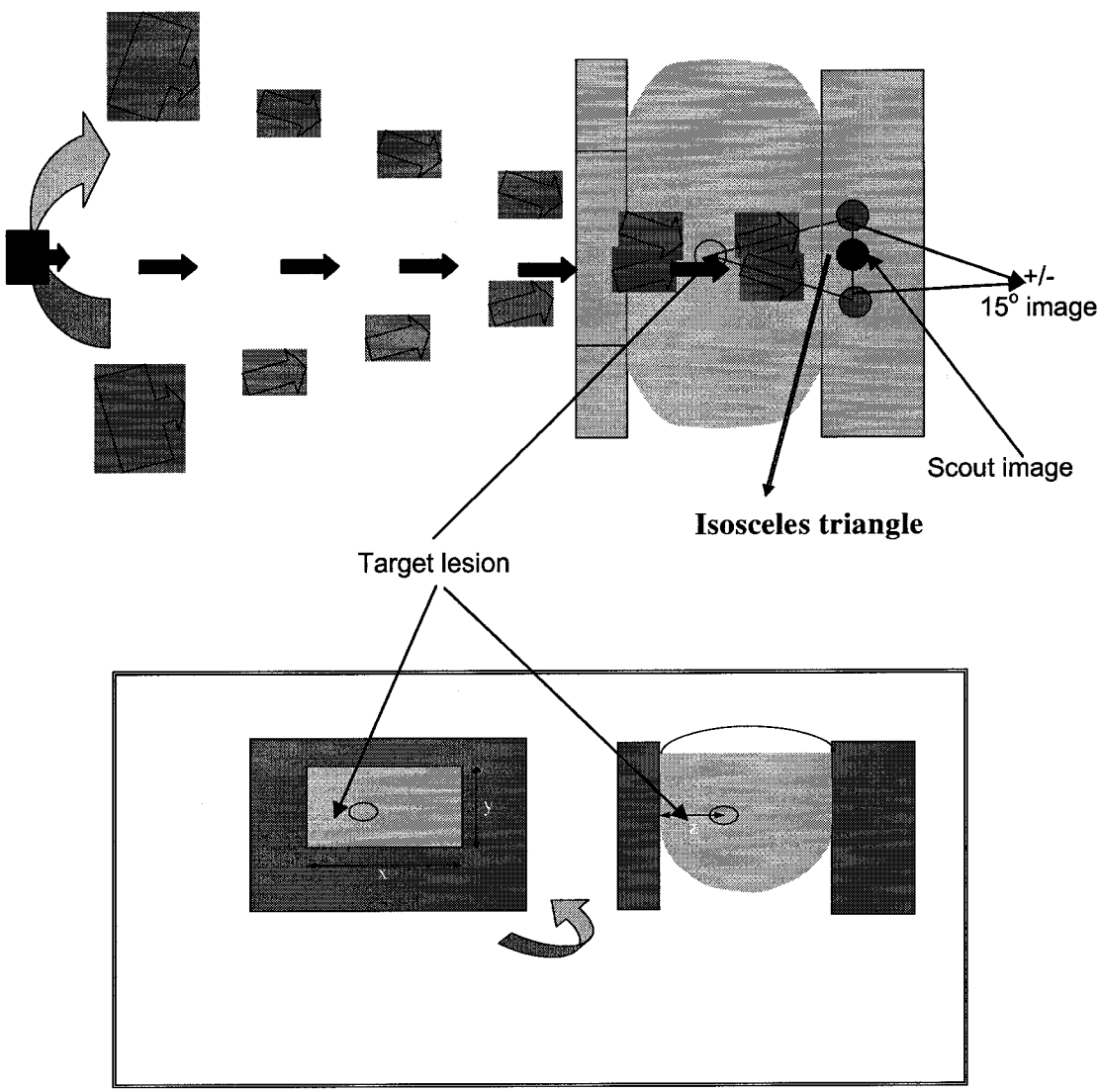
The Operator Workstation is a computer system that is connected to the Digital Image Receptor. The Operator Workstation connects to the ABBI control panel and the display through serial data ports. The Digital Imaging System computer uses DOS, a Disk Operating System, to manage the flow of information to and from the various parts of the system.

The interface to the system is via DOS commands, which can either be typed or selected from menus to perform certain tasks so as to facilitate the viewing of digital mammograms and the measurement and calculation of the horizontal, vertical, and longitudinal location of the lesion.



9. Three Dimensional Stereotactic Imaging

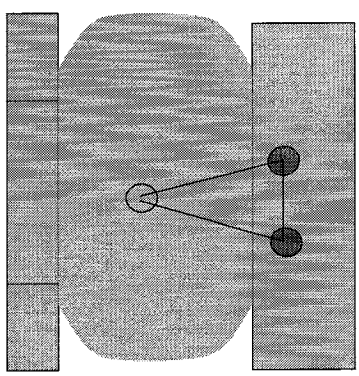
Targets are selected on the ABBI System computer monitor and automatically transferred to needle, marker and cannula, providing placement to within =/- 1mm of accuracy. Stereotactic digital images are then taken at +150 and -150 angles. These data are transmitted to the computer as the X (horizontal) and Y (vertical) dimensions forming an isosceles triangle.



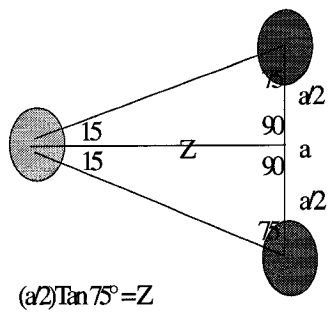
In order to estimate the location of the lesion, the distance between the skin and the lesion is calculated using basic trigonometry. The length of the perpendicular line (z) dividing the triangle's base (a) in half is the distance between the skin and the lesion. This provides the length of the distance from the skin to the lesion. This length is calculated by the trigonometric formula (a/2) Tan 75° = Z.

a. The added option that allows the operator to adjust the intensity of the background and reverse the image to a negative view provides increased detection accuracy.

b. Multiple target positions and a 1 cm round target image facilitate the selection of the center of the lesion, which is required for accurate localization.



Isosceles triangle formed



APPENDIX 6A: ARTICLES USED IN ABBI LITERATURE REVIEW

1

	Journal	Author	Year	Country
1	**AJR**	Smathers	2000	USA
2	**AJR**	Rebner	1999	USA
3	**AJR**	Leibman	1999	USA
4	**Am J Surg**	Matthews	1999	USA
5	**Am J Surg**	D'angelo	1997	USA
6	**Am Surg**	Sheth	1999	USA
7	**Ann Surg Oncol**	Bloomston	1999	USA
8	**nn. Surg Oncol**	Velanowich	1999	USA
9	**Br J Radio**	Damascelli	1998	USA
10	**Breast J**	Ferzli	1999	USA
11	**Breast J**	Kelley	1998	USA
12	**Breast J**	Yang	2000	USA
13	**Can J Surg**	Perelman	2000	Canada/Tor
14	**Eur. Radiol.**	Insausti	2002	Spain
15	**Eur. Radiol.**	Lifrange	2001	Belgium
16	**J Am Coll Surg**	Schwartzberg	2000	Usa
17	**J Am Coll Surg**	Ferzli	1997	Usa
18	**J Gynecol**	Poilpot	2000	France
19	**J Med Liban**	Atallah	2000	Liban
20	**J Surg Onc**	Portincasa	2000	Italy
21	**Pathologe**	Ammann	2000	Germany
22	**Schweiz**	Oertli	1998	Sweden
23	**Surg End**	Ferzli	1997	USA
24	**Surgery**	La Raja	1999	USA
25	**Adv. Anat. Pathol**	Wong	2000	USA
26	**Swiss Surg**	Marti	2000	Sweden

APPENDIX 6B1: ARTICLES REPORTING ABBI ADVERSE EVENTS / COMPLICATIONS

AUTHOR	YEAR	N*	COMPLICATION	#AE	AE	SE	95% CI	
Insausti	2002	255	Wound infection	3	1.18%	0.0068	-0.001	0.025
			Haematoma	4	1.57%	0.0078	0.000	0.031
			Vasovagal	3	1.18%	0.0068	-0.001	0.025
Yang	2000	100	Bleeding	2	2.00%	0.0140	-0.007	0.047
Perelman	2000	34	Vasovagal attack	4	11.76%	0.0553	0.009	0.226
			Haematoma	2	5.88%	0.0404	-0.020	0.138
			Wound infection	1	2.94%	0.0290	-0.027	0.086
			Bruising	1	2.94%	0.0290	-0.027	0.086
			Anxiety attack	1	2.94%	0.0290	-0.027	0.086
			Technical problems	13	38.24%	0.0833	0.219	0.546
Atallah	2000	67	Haematoma	8	11.94%	0.0396	0.042	0.197
Rebner	1999	90	Haematoma	9	10.00%	0.0316	0.038	0.162
			Bleeding	3	3.33%	0.0189	-0.004	0.070
			Wound problems	2	2.22%	0.0155	-0.008	0.053
			Pneumothorax	1	1.11%	0.0110	-0.011	0.033
			Venous thrombosis	1	1.11%	0.0110	-0.011	0.033
Leibman	1999	54	Haematoma	3	5.56%	0.0312	-0.006	0.117
			T-bar fracture	3	5.56%	0.0312	-0.006	0.117
Matthews	1999	110	Haematoma	2	1.82%	0.0127	-0.007	0.043
			Wound infection	1	0.91%	0.0090	-0.009	0.027
Sheth	1999	230	Bleeding	1	0.43%	0.0043	-0.004	0.013
Bloomston	1999	99	Haematoma	2	2.02%	0.0141	-0.008	0.048
			Equip. malfunction	4	4.04%	0.0198	0.002	0.079
Velanowich	1999	104	Technical failure	30	28.85%	0.0444	0.201	0.376
Ferzli	1999	132	Haematoma	2	1.52%	0.0106	-0.006	0.036
			Vasovagal attack	1	0.76%	0.0075	-0.007	0.022
			Technical problems	31	23.48%	0.0369	0.163	0.307
La Raja	1999	127	Haematoma	1	0.79%	0.0078	-0.007	0.023
Damascelli	1998	77	Haematoma	3	3.90%	0.0221	-0.004	0.082
Kelley	1998	654	Haematoma	11	1.68%	0.0050	0.007	0.027
			Cellulites	1	0.15%	0.0015	-0.001	0.005
TOTAL		**2949**		**154**	**5.22%**	**0.0041**	**0.044**	**0.060**

APPENDIX 6B2: STUDIES REPORTING NO ADVERSE EVENTS / COMPLICATIONS

Author	Year	N
Oertli	1998	36
D'Angelo	1997	23
Ferzli	1997	34
Ferzli	1997	54
Portincasa	2000	165
Ammann	2000	40
Marti	2000	144
Schwartzberg	2000	150
Poilpot	2000	33
Lifrange	2001	36
Smathers	2000	101
n (studies without complication)		**816**
Total cases without complication		**2133**
Total cases overall		**2949**
% no complications		**72.33%**

APPENDIX 6C: ADVERSE EVENTS / COMPLICATIONS REPORTED WITH THE ABBI

Complications	**# cases**	**%AE**	**%n**	**SD**	**SE**	**95% CI**	
Technical failure	81	52.60%	2.75%	0.16	0.003	0.022	0.033
Adverse Events	**# cases**	**%AE**	**%n**	**SD**	**SE**	**95% CI**	
Haematoma	47	30.52%	1.59%	0.13	0.002	0.011	0.020
Vasovagal	8	5.19%	0.27%	0.05	0.001	0.001	0.005
Wound infection	7	4.55%	0.24%	0.05	0.001	0.001	0.004
Bleeding	6	3.90%	0.20%	0.05	0.001	0.000	0.004
Anxiety attack	1	0.65%	0.03%	0.02	0.000	0.000	0.001
Bruising	1	0.65%	0.03%	0.02	0.000	0.000	0.001
Cellulites	1	0.65%	0.03%	0.02	0.000	0.000	0.001
Pneumothorax	1	0.65%	0.03%	0.02	0.000	0.000	0.001
Venous thrombosis	1	0.65%	0.03%	0.02	0.000	0.000	0.001
Total complications	**154**		2.48%	0.16	0.003	0.019	0.030
Overall sample size (N)	**2949**						

APPENDIX 6D: ARTICLES REPORTING MARGIN STATUS AFTER THE ABBI

No.	AUTHOR	N. Pts	ABBIs	Ca	Clear Margins	p-value	SE	95% Confidence Intervals	
1	Perelman	34	34	7	0	0.0000	0.0000	0.0000	0.0000
2	Atallah	67	67	12	67	1.0000	0.0000	1.0000	1.0000
3	Smathers	101	101	27	15	0.1485	0.0354	0.0792	0.2179
4	Schwartzberg	150	150	39	150	1.0000	0.0000	1.0000	1.0000
5	Ammann	40	40	12	3	0.0750	0.0416	-0.0066	0.1566
7	Marti	144	135	32	23	0.1704	0.0313	0.1090	0.2318
9	Rebner	89	71	11	32	0.4507	0.0527	0.3473	0.5541
10	Leibman	53	53	7	7	0.1321	0.0465	0.0409	0.2232
11	Yang	80	80	17	8	0.1000	0.0335	0.0343	0.1657
13	Bloomston	99	99	18	3	0.0303	0.0172	-0.0035	0.0641
16	Matthews	107	110	28	20	0.1818	0.0373	0.1087	0.2549
total		**964**	**940**	**210**	**328**	**0.349**	**0.015**	**0.3188**	**0.3790**

APPENDIX 6E: ARTICLES REPORTING SUBSEQUENT SUPPLEMENTAL SURGERY AFTER THE ABBI

AUTHOR	YEAR	ABBI	Supplemental Surgery						
			Lumpectomy	MRM*	n	p-value	SE	95% Confidence Intervals	
Perelman	2000	34	Unspecified	Unspecified	4	0.12	0.055	0.009	0.226
Atallah	2000	67	Unspecified	Unspecified	12	0.18	0.047	0.087	0.271
Rebner	1999	90	5	2	7	0.08	0.028	0.022	0.133
Leibman	1999	54	4	2	6	0.11	0.043	0.027	0.195
Matthews	1999	110	14	5	19	0.17	0.036	0.102	0.243
Bloomston	1999	99	12	5	17	0.17	0.038	0.097	0.246
Ferzli	1999	132	Unspecified	Unspecified	20	0.15	0.031	0.090	0.213
Damascelli	1998	77	Unspecified	Unspecified	32	0.42	0.056	0.306	0.526
Total		**663**			**117**	**0.18**	**0.015**	**0.151**	**0.209**

*** MRM = Modified Radical Mastectomy**

APPENDIX 6F: SUMMARY OF OVERALL CLINICAL RESULTS OF COMPARATIVE STUDIES

Study	N (patients)			Outcomes	Number of procedures (%)	
	ABBI	WL	CNB		ABBI	WL
Velanovich et al 1999	104	520	245	**Positive margins (cancer)** **Reexcision rate** **Technical success** **Sensitivity** **Specificity** **Residual cancer rate**	63.6% 7.5% 92.5% 100% 100% 71.4%	50.9% 23.5% 98.7% NA NA 70.4%
D'Angelo et al 1997	23	23		**Malignant** **Positive margins (cancer)** **Mean procedure time** **Mean blood loss** **Residual abnormalities** **Residual cancer** **Cost**	21.7% 100% 18 (9–38) min. 14 (9.7) cc 8.7% 60.0% 1500 USD	21.7% 100% NA 20 (9.8) cc NA 40.0% 2500 USD

NA = Not Available,

WL = Wire Localization

APPENDIX 6G: COMPARATIVE PATIENT SATISFACTION AND COSMETIC RESULTS

Study	N (patients)		Outcomes	Number of procedures (%)	
	ABBI	WL		ABBI	WL
D'Angelo	23	23	**Subjective comfort** Excellent Good Poor	 21 2 1	 23
			Cosmetic satisfaction Excellent Acceptable	 23 0	 0 23
Chun	20	20	**Cosmetic satisfaction** Excellent Acceptable Unacceptable	 95% 5% 0%	 25% 55% 20%
			Overall satisfaction Satisfied Dissatisfied	 75% 25%	 90% 10%

APPENDIX 7: PATIENT INFORMATION AND CONSENT FORM

TITLE OF THE STUDY:

DEVELOPMENT & EVALUATION OF THE ADVANCED BREAST BIOPSY INSTRUMENTATION (ABBI) SYSTEM

NATURE AND PURPOSE OF THE STUDY

The purpose of this research study is to look at the role of the Advanced Breast Biopsy Instrumentation (ABBI) procedure in performing a breast biopsy using an image-guide machine (similar to a mammogram; a breast X-ray). Recently, you have had a mammogram where an abnormal area was found. This abnormal area may or may not be cancer, but is questionable enough to perform a biopsy (remove and diagnose the breast tissue under the microscope). This biopsy may be performed in a number of ways. Or you may already have a diagnosis of cancer made with a stereotactic **(using a needle)** or ultrasound-directed breast biopsy. Since this abnormal area is not palpable (you or your doctor cannot feel it), an image-guided biopsy needs to be done. The ABBI procedure is a type of image-guided biopsy where the whole area can be removed with a minimally invasive approach. **This method used for a breast biopsy is a diagnostic procedure accepted in Canada and in the United States.**

STUDY PROCEDURE

Normally, the day of the ABBI procedure you will be asked to come to the Radiology Department, where you will have your breast imaged to see if you are a candidate for this type of biopsy. The doctor will then present this project to you which is to evaluate the ABBI procedure for therapeutic purposes. You will then have a reflexion period

and if you decide to participate in the study and after signing this informed consent, a pill that you take by mouth may be given to you to help calm your nerves during the biopsy. You will be asked to lie on your stomach on a specially designed raised padded table, making sure you are as comfortable as possible. Your breast will be placed through a round opening in the table. The table is then raised so the radiologist and surgeon can work from below. Slight pressure is then applied to the breast and mammographic (X-ray) images are used to find the abnormal area. Next, the doctor will use a small needle to numb the breast to inject a local anaesthetic (you will feel a stinging sensation and some burning as the anaesthetic is injected). A small cut approximately 2.5 cm (1-1 ½ inch) is made in your breast then a core of tissue is then removed using a special tool called a "cannula".

The pressure paddle will be released from your breast, you will roll onto your back, and the wound will be closed with sutures. You will be seen for a follow-up visit with your doctor the following week to discuss the pathology and to have your wound examined.

After the biopsy, your breast tissue will be sent to the X-ray department to make sure that the questionable area on mammogram has been removed. After the tissue is X-rayed, it is then sent to the pathology department where a doctor will look at the tissue under the microscope for diagnosis and margin determination.

You will be able to relax for as long as you need. You can leave the hospital the same day, when you feel ready. You may want to have a friend accompany you home.

The Advanced Breast Biopsy Instrumentation or ABBI is a minimally invasive procedure, which is performed under local anesthesia. Patients who have been submitted to an ABBI biopsy report the feeling of a tingling or burning sensation upon administration of the local anesthetic.

The procedure is tolerated very well by 98.5% of the patients. Under 10% have reported minimum pain and less than 2% have complained of neck discomfort. If at any time during the procedure you feel pain the surgeon will locally inject more anesthetic. The topical anesthetic used is "Xylocaine".

The ABBI biopsy, if positive for cancer, will be followed by a standard lumpectomy (removing the tumour with a rim of normal breast tissue around it) or mastectomy (removal of the breast). Sentinel lymph node (SLN), the first lymph nodes of the axillary basin under the arm) biopsy or complete lymph node dissection (take out all the lymph nodes) will be used to make sure the cancer has not spread to the lymph nodes under the arm. This is performed in the operating room under general anaesthesia (you are put to sleep) and will be covered with a separate informed consent. These choices are the standard of surgical care for women diagnosed with breast cancer.

After your surgery, your doctor will follow you on a routine basis. The time you will need to spend in this study will be about 1 hour for the ABBI biopsy. If your pathology is positive for breast cancer, your doctor may require follow-up visits every 3 months for the first year, then every 6 months for the following 2 years, then after that, you will be seen every year.

All women who have a lumpectomy to treat their tumour will undergo 4-6 weeks of radiation therapy. These treatments are necessary to complete your breast preservation treatment.

If you wish, you can talk to the study doctor **or** to your personal doctor about what you should do. Talking things over can help you make the right choice.

Plan of Treatment

Your **regular medical treatment** will not actually be part of the research study but will prepare you for the study. This treatment will include:

Bilateral Mammograms and Breast Biopsy

The **experimental treatment** that you will receive by taking part in this research study is:

The evaluation of margins around the ABBI breast biopsy.

Storage of Blood and/or Tissue Samples

By participating in this research, blood and/or other body tissues will be removed from you, will be analyzed and used by the Investigators and/or sponsors. The amount of blood removed is approximately 10-15 ml (2-3 teaspoons). **With regard to the tissues, please see the attached consent form.**

Benefits of Being a Part of this Research Study

We cannot tell you whether you will or will not benefit from taking part in this study. On the other hand, by taking part in this research study, you may increase our overall knowledge of your disease and how to treat future patients. The findings of the study may eventually result in a more conservative approach to breast cancer, similar to the discovery that lumpectomy was just as effective as mastectomy in treating breast cancer and the SLN biopsy was more accurate than the more radical axillary dissection in staging breast cancer. Performing and ABBI excision of your tumour has the potential of removing less of the healthy breast tissue and causing less of a cosmetic deformity.

Risks of Being a Part of this Research Study

There is no additional risk involved with the study since you have been advised that there is an area of your mammogram that needs to be biopsied and the ABBI procedure is an approved breast biopsy method. In addition, the ABBI breast biopsy will be followed by the standard treatment for women who want to save their breast, **or**

a lumpectomy or mastectomy followed by a SLN biopsy **if this is your choice**. You may have side effects from the standard treatment of your disease. These possible complications may occur with breast cancer surgery, and include infection, bleeding, and problems with wound healing. The potential complications of the ABBI procedure are the same as with any surgical procedure.

All women treated with lumpectomy have 4-6 weeks of radiation therapy to the remainder of the breast to complete the treatment.

The study doctors will immediately tell you if during the study they discover that the ABBI procedure causes other new and unknown side effects. If the new findings make it unwise for you to continue, the doctors will stop your treatment. You will then be offered other suitable treatment for your disease.

Alternatives of Being Part of this Research Study

Alternatives of being part of this research study are:

There are three possible methods to sample/biopsy abnormalities that are discovered on mammograms and are not palpable.

1. **Stereotactic Core Biopsy (ultrasound or mammogram)** – A similar table is used to sample the breast in and around an abnormal area. Smaller core needles are used for this procedure, but additional mammograms are needed. The advantage of this technique is that just a puncture wound is made in the breast about 2-3 mm in size. The disadvantage of this procedure is that the biopsy is just a sampling and the entire lesion is not removed. There is a possibility that the right area may not be sampled (sampling error) or the specimen obtained may not be adequate to make the diagnosis.
2. **ABBI Breast Biopsy** – The advantage of this technique over the stereotactic core is that the entire abnormality is removed and thus sampling errors should not

occur. The advantage over the needle directed excisional biopsy is that the entire abnormal area may be removed. In addition, less tissue is removed compared to needle directed excisional biopsy, thus preserving more normal and healthy breast tissue. The disadvantage is that it is a larger incision in the breast 25-40 mm, (1-1 ½ inches) is needed compared to a stereotactic core biopsy.

3. **Needle Directed Excisional Biopsy** - This technique involves a trip to the radiology suite where a guide wire is placed under local anaesthesia. The patient is then brought to the operating room and under IV sedation or general anaesthesia, the surgeon biopsies the breast tissue. The advantage of this method over a stereotactic core is that the entire lesion is removed, but at the expense of making 50-100 mm (2-4 inch) incision in the breast. It is also more costly than the other two biopsies, since a formal operating room is needed, with anaesthesia.

Pregnant women cannot participate in this study. So if you are pregnant, become pregnant, or breast feeding while taking part in this research study, tell your study doctor immediately.

APPENDIX 8: ADVANCED BREAST BIOPSY INSTRUMENTATION: CASE REPORT FORM

M RN: _____ ***Date of Birth:*** ___/___/___ (YY/MM/DD)

ETHNIC BACKGROUND:

- ☐ **CAUCASIAN**
- ☐ **HISPANIC**
- ☐ **ASIAN**
- ☐ **AFRICAN AMERICAN**
- ☐ **INUIT**
- ☐ **OTHER: SPECIFY**_____

MEDICAL HISTORY UNRELATED TO BREAST:

Medical Condition: Year Management:

_____ _____ _____

_____ _____ _____

MEDICAL HISTORY RELATED TO BREAST:

Medical Condition: Year Management:

_____ _____ _____

_____ _____ _____

Mammographic Evaluation:

Date of Last Mammogram: ____/____/____ (MM/DD/YY)

Level of suspicion:

- ☐ Category I
- ☐ Category II
- ☐ Category III
- ☐ Category IV

Indication for Procedure:

- ☐ Soft Tissue Nodule
- ☐ Microcalcifications
- ☐ Combined Soft Tissue Nodule & Microcalcifications

Quadrant:

- ☐ UO
- ☐ UI
- ☐ LO
- ☐ LI
- ☐ C

Mammographic Size of Lesion: _____(mm):

Digital Size of Lesion: _____(mm)

ABBI approach:

- ☐ Lateral
- ☐ Superior
- ☐ Oblique
- ☐ Inferior
- ☐ Medial

Breast Compression: _____ (mm)

Z-axis_____ (mm)

Estimated Blood Loss: _____ (cc)

Posterior Margin: _____ (mm)

A = Time of 1st specimen image: ____:____ (24 hour format)

B = Time of final stereo image: ____:____ (24 hour format)

Procedure time = B – A = _____ min.

Post-operative breast image:

NEGATIVE = No residual tumour detected ☐

POSITIVE = Residual tumour detected ☐

Specimen image:

NEGATIVE = No tumour detected ☐

POSITIVE = Tumour detected ☐

Macroscopic (gross) margins of the excised lesion:

Under macroscopic inspection the tumour is excised within:

☐ **NEGATIVE = healthy margins**

☐ **POSITIVE = involved margins**

Re-excision performed:

NO ☐

YES ☐

Estimated Blood Loss: _____ **(cc)**

Histological Assessment:

HISTOLOGIC DIAGNOSIS:

- ☐ **Fibrocystic Breast**
- ☐ **Benign Tumour**
- ☐ **Atypic Hyperplasia**
- ☐ **DCIS**
- ☐ **Infiltrating Ductal Ca**
- ☐ **DCIS + Infiltrating Ductal Ca**
- ☐ **LCIS + Lobular Invasive Focally**

Size Of Lesion: _____(mm)

Size Of Specimen: _____(mm)

Microscopic i margins of the excised lesion:

Under <u>microscopic</u> inspection the tumour is excised within:

- ☐ **NEGATIVE = (≥ 1 mm healthy peripheral tissue)**

  Safe Surgical Margins

- ☐ **POSITIVE = (< 1 mm healthy peripheral tissue)**

  Involved (invaded) margins

Post-Operative Therapy:

☐ SUPPLEMENTARY PARTIAL MASTECTOMY

☐ NO SUPPLEMENTARY SURGERY REQUIRED

Adjuvant Therapy:

☐ CHEMOTHERAPY

☐ RADIOTHERAPY

☐ TAMOXIPHEN

Follow-Up:

DATE: _____/_____/_____ (MM/DD/YY)

Recurrence:

☐ **NO**

☐ **YES (IPSILATERAL BREAST)**

☐ **YES (CONTRALATERAL BREAST)**

☐ **REGIONAL METASTASIS – AXILLARY LYMPH NODES**

☐ **DISTANT METASTASIS (specify): _____**

APPENDIX 9: PATIENT SATISFACTION SURVEY - QUESTIONNAIRE

	%	95% Confidence Intervals	
1. **Reason for choice of center:**			
a. Physician referral	85	78.0	92.0
b. Friend / family member	15	8.0	22.0
c. Internet / media	0	0.0	0.0
d. Other	0	0.0	0.0
2. **Understanding of other therapeutic or diagnostic options:**			
a. Excellent	5	0.7	9.3
b. Very good	65	55.7	74.3
c. Good	15	8.0	22.0
d. Moderate	15	8.0	22.0
e. Poor	0		
3. **Knowledge of the ABBI and wire localization excisional biopsy excisional biopsy procedures**			
a. Excellent	2	-0.7	4.7
b. Very good	45	35.2	54.8
c. Good	15	8.0	22.0
d. Moderate	25	16.5	33.5
e. Poor	13	6.4	19.6
4. **Reasons for choosing the ABBI:**			
a. Physician trust	65	55.7	74.3
b. Previous experience with the ABBI	4	0.2	7.8
c. Previous bad experience with wire localization excisional biopsy excisional biopsy	6	1.3	10.7
d. Friend / family member good experience with the ABBI	1	-1.0	3.0
e. Friend / family member bad experience with wire localization excisional biopsy excisional biopsy	1	-1.0	3.0
f. Preference for local anesthesia vs general	20	12.2	27.8
g. Shorter waiting list	3	-0.3	6.3
5. **Knowledge of advantages and disadvantages of the ABBI:**			
a. Excellent	2	-0.7	4.7
b. Very good	33	23.8	42.2
c. Good	30	21.0	39.0
d. Moderate	22	13.9	30.1
e. Poor	13	6.4	19.6
6. **Patient satisfaction in the facility:**			
a. Excellent	35	25.7	44.3
b. Very good	40	30.4	49.6
c. Good	20	12.2	27.8
d. Moderate	5	0.7	9.3

e. Poor	0		
7. **Duration of waiting between scheduling and procedure:**			
a. 1 – 2 weeks	45	35.2	54.8
b. 2 – 4 weeks	35	25.7	44.3
c. 5 – 8 weeks	20	12.2	27.8
d. 9 – 12 weeks	0		
e. 12 – 16 weeks	0		
f. more than 16 weeks	0		
8. **Duration of waiting between procedure and results:**			
a. 1 – 2 weeks	51	41.2	60.8
b. 2 – 4 weeks	49	39.2	58.8
c. 5 – 8 weeks	0		
d. 9 – 12 weeks	0		
e. 12 – 16 weeks	0		
f. 16 weeks	0		
9. **Comfort during procedure:**			
a. Excellent	11	4.9	17.1
b. Very good	57	47.3	66.7
c. Good	12	5.6	18.4
d. Moderate	13	6.4	19.6
e. Poor	7	2.0	12.0
10. **Comfort after the procedure:**			
a. Excellent	6	1.3	10.7
b. Very good	63	53.5	72.5
c. Good	21	13.0	29.0
d. Moderate	6	1.3	10.7
e. Poor	4	0.2	7.8
11. **Satisfaction with procedure:**			
a. Excellent	23	14.8	31.2
b. Very good	51	41.2	60.8
c. Good	18	10.5	25.5
d. Moderate	1	-1.0	3.0
e. Poor	7	2.0	12.0
12. **Regrets for choosing the ABBI:**			
a. Many	8	2.7	13.3
b. Few	12	5.6	18.4
c. None	80	72.2	87.8
13. **Duration of hospital stay after the surgery:**			
a. 30 minutes or less	78	69.9	86.1
b. 30 min. to 1 hour	17	9.6	24.4
c. 1 – 2 hours	4	0.2	7.8

d. 2 – 5 hours	1	-1.0	3.0
e. 5 – 10 hours	0		
f. 1 – 2 days	0		
14. **Time to normal level of activity:**			
a. Same day	49	39.2	58.8
b. 1 – 2 days	23	14.8	31.2
c. 2 – 5 days	18	10.5	25.5
d. 5 – 10 days	10	4.1	15.9
e. more than 10 days	0		

APPENDIX 10: UNIT COSTS PER ABBI AND PER WIRE LOCALIZATION OPEN BIOPSY

COST CATEGORIES	ABBI™	Excisional Breast Biopsy	
		Needle Loc (Radiology)	Excisional (OR)
RADIOLOGY	N/A	$239.36	
Staffing/Supplies/Equip.			
PRE-SURGERY CLINIC	N/A		$7.80
Staffing/Supplies/ Meds/Equip.			
OPERATING ROOM	N/A		$548.40
Staffing/Supplies/ Anaesthesia/Equip.			
PACU	N/A		$968.84
Staffing/Supplies/ Meds/Equip.			
SURGICAL DAY CARE	N/A		$176.00
Staffing/Supplies/ Meds/Equip.			
ABBI™ COSTS	$646.28		N/A
Breast Centre Costs (Staffing/Supplies)			
PHARMACY	$6.74		$4.72
Staffing/Supplies/Equip.			
LABORATORY	N/A		$81.90
Staffing/Supplies/Equip.			
TOTAL	**$653.02**		**$2,027.02**

APPENDIX 11: ESTIMATES USED FOR COST ANALYSIS

Point Estimate					
	ABBI	**WL**			
Number of Cases	1000	1000			
Cost per Case	$653	$2,027			
Total Cost For 1,000 Cases	$653,000	$2,027,000			
Supplemental Surgery Rate	14.9%	30.3%			
Number with Supplemental Surgery	97.297	614.181			
Cost per case of Supplemental Surgery	$7,697	$7,697			
Total Cost for all Supplemental Surgery	$748,895	$4,727,351			
Total for Management	$1,401,895	$6,754,351		$5,352,456	$5,352
	$1,402	$6,754		-$5,352	
Worst Case					
	ABBI	WL			
Number of Cases	1000	1000			
Cost per Case	$653	$2,027			
Total Cost For 1,000 Cases	$653,000	$2,027,000			
Supplemental Surgery Rate	17.2%	27.8%			
Number with Supplemental Surgery	112.316	563.506			
Cost per case of Supplemental Surgery	$7,697	$7,697			
Total Cost for all Supplemental Surgery	$864,496	$4,337,306			
Total for Management	$1,517,496	$6,364,306		$4,846,809	$4,847
	$1,517	$6,364		-$4,847	
Intermediate Case 1					
	ABBI	**WL**			
Number of Cases	1000	1000			
Cost per Case	$653	$2,027			
Total Cost For 1,000 Cases	$653,000	$2,027,000			

Supplemental Surgery Rate	12.7%	27.8%			
Number with Supplemental Surgery	82.931	563.506			
Cost per case of Supplemental Surgery	$7,697	$7,697			
Total Cost for all Supplemental Surgery	$638,320	$4,337,306			
Total for Management	$1,291,320	$6,364,306		$5,072,986	$5,073
	$1,291	$6,364		-$5,073	
Intermediate Case 2					
	ABBI	**WL**			
Number of Cases	1000	1000			
Cost per Case	$653	$2,027			
Total Cost For 1,000 Cases	$653,000	$2,027,000			
Supplemental Surgery Rate	17.2%	32.8%			
Number with Supplemental Surgery	112.316	664.856			
Cost per case of Supplemental Surgery	$7,697	$7,697			
Total Cost for all Supplemental Surgery	$864,496	$5,117,397			
Total for Management	$1,517,496	$7,144,397		$5,626,900	$5,627
	$1,517	$7,144		-$5,627	
Best Case 2					
	ABBI	**WL**			
Number of Cases	1000	1000			
Cost per Case	$653	$2,027			
Total Cost For 1,000 Cases	$653,000	$2,027,000			
Supplemental Surgery Rate	12.7%	32.8%			
Number with Supplemental Surgery	82.931	664.856			
Cost per case of Supplemental Surgery	$7,697	$7,697			
Total Cost for all Supplemental Surgery	$638,320	$5,117,397			

Total for Management	$1,291,320	$7,144,397		$5,853,077	$5,853
	$1,291	$7,144		-$5,853	

APPENDIX 12: ABBI SURGICAL METHOD DESCRIPTION

The following section provides a detailed technical description of the ABBI method. This description is included here because it may be useful to the reader to appreciate the ABBI procedure.

All ABBI patients had agreed and given their written consent to undergo the procedure. All ABBI biopsies were performed at the day-surgery clinic under local anaesthesia. Prior to the procedure each patient was briefed about the ABBI equipment and was then given a description of the procedure.

The ABBI table is draped and the patient's breast sterilized according to standard protocol. The patient lies prone on the ABBI table. Special cushions are provided for additional comfort. The affected breast is allowed to hang through an opening in the table and is compressed between the compression plate and the image receptor.

Once the patient is positioned, a scout (straight forward) image is taken to confirm that the lesion is located at the center of the surgical window. The approach requiring the shortest distance from the skin to the lesion is chosen, in order to minimize the amount of tissue removed. Stereotactic digital images are then taken at +150 and -150 angles and the lesion is localized within the three dimensions described earlier. These three dimensions are transmitted to the ABBI panel and the ABBI device is mounted on the LoRad table and electronically moved to the X

and Y positions of the target. At this point the preparation for the biopsy is completed and the surgical procedure will be initiated.

During the procedure the surgeon informed the patient of each step to follow and warned her before any expected discomfort so as to avoid movement. Under local anaesthesia a 2mm. skin incision is made upon target X and Y-axis and the 16G-needle guide is inserted into the breast, to the longitudinal depth (Z-axis) of the target lesion. At this moment, an image is taken of the breast in order to confirm that the location of the ejected needle is indeed less than 1 mm from the target and ideally at the center of the target. Adjustments are possible at this point in the procedure if they are required in order to position the needle more accurately. Once the proper position is confirmed, the T-crossbar is deployed to stabilize the needle in the tumor.

At this time, more local anaesthesia is given and the incision is extended to 3 cm. (1.5 cm. on either side of the needle). Skin flaps are adequately prepared and deep tissue anaesthesia is injected around the periphery of the cannula. The ABBI coring device is then slowly inserted into the breast as the circular blade cuts through the tissue. The cannula is advanced beyond the needle and T-crossbar. At this point an optional final confirmation image can be taken before the specimen is completely transected. The wire snare is activated and transects the distal end of the specimen, while cautery is applied to the surrounding tissue. The tissue inside the cannula is protected from cautery to prevent damage.

After the removal of the ABBI device from the breast, digital images of the breast are taken and examined carefully for residual tumor or calcifications, which may be an indication of residual disease. Removing detected calcifications may help achieve a complete excision of the lesion and avoid further supplementary surgery in the future. The surgical cavity remains open and is easily examined under direct vision for any suspicious findings, such as calcifications or residual tumor, which may need to be excised. After satisfactory inspection the surgical cavity is tamponaged and the incision covered. The patient is then turned to the supine position and is allowed to rest while the excised specimen is imaged by digital mammography and reviewed by the surgeon and radiologist to confirm that the lesion is present and excised within acceptable gross margins. Haemostasis and subcuticular suturing of the incision complete the ABBI procedure.

The pathologist receives the unfragmented specimen in the ABBI room where the specimen images are viewed in order to ensure that the macroscopic margins (the outer margins of the specimen as seen by the unaided eye) for findings suspicious of malignancy (such as calcifications or parts of the tumor that have been incompletely excised). This is followed by orienting the edges of the specimen as it was previously located in the breast as lateral, medial, superior and inferior. This will help the pathologist orient the location of any residual tumor found in the microscopic margins (assessment of the exterior margins of

the excised specimen for malignancy at the cellular level with the aid of a microscope) of the specimen. Whenever possible a frozen section is performed for a preliminary diagnosis. Further histological analysis of the malignant tumors excised follows, reporting the tumor type and size, as well as the microscopic margins.

The patients were asked to rest for 10- 15 minutes before leaving the clinic. Before their departure they were asked to answer a patient satisfaction questionnaire.

APPENDIX 13: SENTINEL LYMPPH NODE BIOPSY LITERATURE REVIEW

N	JOURNAL		AUTHOR	YEAR	Country	DESIGN	PTS	SLNB	BOTH	%FN
1	jama	**198**	**ALBERTINI**	1996	USA	prospective	62	57	62	0
2	n z med j	**43**	**ALLEN**	2001	Canada	prospective	36	34	36	0
3	breast cancer	**232**	**BADGWELL**	2002	USA	retrospective	222	222		3.1
4	minerva chir	**203**	**BARILLARI**	2002	Italy	prospective	60	60	60	2
5	ann surg oncol	**204**	**BARNWELL**	1998	USA	prospective	42	38	42	0
6	j surg oncol	**206**	**BARRANGER**	2004	France	retrospective	185	180	180	3.2
7	breast j	**207**	**BEITSCH**	2001	USA	prospective	85	85		16
8	ann surg oncol	**208**	**BLAND**	2002	USA					
9	j am coll surg	**191**	**BORGSTEIN**	1998	Netherlands	prospective	130	122	122	1.7
10	breast j	**209**	**BRADY**	2002	USA	prospective	14	13		0
11	br j surg	**247**	**BRANAGAN**	2002	UK	prospective				
12	am j surg	**227**	**BURAK**	2002	USA	prospective	96			
13	tumori	**210**	**CARCOFORO**	2002	Italy	prospective	210			
14	am j surg	**242**	**CHAO**	2001	USA	retrospective	203			8
15	breast j	**211**	**COX**	2002	USA	prospective	1352	1352		
16	int j oncol	**224**	**CREAGER**	2002	USA	retrospective	678	21	23	6
17	J Nucl Med	**196**	**DE CICCO**	1998	Italy					
18	j exp clin cancer	**249**	**D'EREDITA**	2001	Italy	prospective	80	80	32	3.8
19	world j surg	**248**	**D'EREDITA**	2003	Italy	prospective	115	109	59	5.9
20	j surg oncol	**200**	**GIPPONI**	2004	Italy	prospective	334	326	153	8.6
21	J Clin Oncol	**218**	**GIULIANO**	2000	USA	propsective	133	132		
22	jpn j clin oncol	**215**	**IMOTO**	1999	Japan	prospective	88	65		6
23	surgery	**219**	**ISHIDA**	2002	Japan	prospective	44	42	44	2
24	breast j	**220**	**ISHIKAWA**	2002	Japan					
25	am j surg	**221**	**JADERBORG**	1999	USA	prospective	91	64	67	7.8
26	arch surg	**222**	**KAMATH**	2001	USA	prospective	101			
27	ann surg oncol	**223**	**KANE**	2001	USA	prospective	150	150		46
28	cancer	**225**	**LEE**	2002	USA	prospective	65			
29	j clin pathol	**226**	**LEERS**	2002	Netherlands	retrospective	257			
30	radiology	**227**	**LIBERMAN**	1999	USA	retrospective	33			9
31	Ann Surg.	**241**	**MCMASTERS**	2001	USA	prospective	2203			7.8
32	breast ca	**217**	**NOGUCHI**	2000	Japan	prospective	126	123		0

33	j am coll surg	**250**	**O'HEA**	1998	USA	prospective	60	59	59	5
34	j am coll surg	**228**	**OLSON**	2000	USA	prospective	223	200	223	5
35	Eur. J Nucl Med	**197**	**PAGANELLI**	1998	Italy	retrospective				5
36	int j biol markers	**229**	**PELEY**	2001	Hungary	prospective	68	68	68	21
37	tumori	**230**	**PELOSI**	2002	Italy	prospective	201	194		
38	am surg	**216**	**PENDAS**	1999	USA	prospective	478	466		
39	j am coll surg	**231**	**PORT**	2002	USA	retrospective	32	24		
40	Br J Cancer	**201**	**REITSAMER**	2004	Austria	Prospective	333	358		
41	am j surg	**233**	**SACHDEV**	2002	USA	prospective	212			
43	jpn j clin oncol	**234**	**SATO**	2001	Japan	prospective	110			
42	breast j	**235**	**SATO**	2001	Japan	prospective	75	74		0
44	oncologist	**236**	**SCHLAG**	2000	Germany	prospective	146	146		4
45	j surg oncol	**214**	**SCHRENK**	2001	Austria	prospective	247	227		
47	j surg oncol	**237**	**SCHRENK**	2002	Austria	prospective	263			
46	Rozhl Chir.	**238**	**SCHRENK**	2005	Austria	retrospective	2326			15.6
48	J Am Coll Surg	**240**	**SCHRENK**	2003	USA	retrospective	3501	3501		8
49	surgery	**239**	**SHIMAZU**	2002	Japan	prospective	155		93	5.6
50	ann surg oncol	**245**	**SHIVERS**	2002	USA	prospective	965		965	4
51	Ann surg	**243**	**TAFRA**	2001	USA	prospective	529			13
52	breast ca res	**246**	**TSUGAWA**	2000	Japan	prospective	48	48	48	5
54	j natl ca instit	**230**	**VERONESI**	1999	Italy	prospective	376	371	371	6.7
53	lancet	**205**	**VERONESI**	1997	Italy	prospective	163	163		2.5
55	jpn j clin oncol	**244**	**WADA**	2003	Japan	retrospective	569	569	16	
56	j am coll surg	**212**	**WONG**	2001	USA	prospective	1436	1287	1287	4.3
58	breast j	**202**	**WONG**	2002	USA	prospective	2206			
57	am surg	**212**	**WONG**	2002	USA	prospective	2206	2206		

APPENDIX 14: SENTINEL LYMPPH NODE BIOPSY LITERATURE REVIEW % - FALSE NEGATIVE

ref.#	JOURNAL	AUTHOR	YEAR	Country	DESIGN	PTS	SLNB	%FN
43	n z med j	ALLEN	2001	Canada	prospective	36	34	0
191	j am coll surg	BORGSTEIN	1998	Netherlands	prospective	130	122	1.7
198	jama	ALBERTINI	1996	USA	prospective	62	57	0
200	j surg oncol	GIPPONI	2004	Italy	prospective	334	326	8.6
203	minerva chir	BARILLARI	2002	Italy	prospective	60	60	2
204	ann surg oncol	BARNWELL	1998	USA	prospective	42	38	0
205	lancet	VERONESI	1997	Italy	prospective	163	163	2.5
206	j surg oncol	BARRANGER	2004	France	retrospective	185	180	3.2
207	breast j	BEITSCH	2001	USA	prospective	85	85	16
209	breast j	BRADY	2002	USA	prospective	14	13	0
212	j am coll surg	WONG	2001	USA	prospective	1436	1287	4.3
215	jpn j clin oncol	IMOTO	1999	Japan	prospective	88	65	6
217	breast ca	NOGUCHI	2000	Japan	prospective	126	123	0
219	surgery	ISHIDA	2002	Japan	prospective	44	42	2
221	am j surg	JADERBORG	1999	USA	prospective	91	64	7.8
223	ann surg oncol	KANE	2001	USA	prospective	150	150	46
224	int j oncol	CREAGER	2002	USA	retrospective	678	21	6
227	radiology	LIBERMAN	1999	USA	retrospective	33		9
228	j am coll surg	OLSON	2000	USA	prospective	223	200	5
229	int j biol markers	PELEY	2001	Hungary	prospective	68	68	21
230	j natl ca instit	VERONESI	1999	239-242,245,246,248-250	prospective	376	371	6.7
232	breast cancer	BADGWELL	2002	USA	retrospective	222	222	3.1
235	breast j	SATO	2001	Japan	prospective	75	74	0
236	oncologist	SCHLAG	2000	Germany	prospective	146	146	4
238	Rozhl Chir.	SCHRENK	2005	Austria	retrospective	2326		15.6
239	surgery	SHIMAZU	2002	Japan	prospective	155		5.6
240	J Am Coll Surg	SCHRENK	2003	USA	retrospective	3501	3501	8
241	Ann Surg.	MCMASTERS	2001	USA	prospective	2203		7.8
242	am j surg	CHAO	2001	USA	retrospective	203		8
243	Ann surg	TAFRA	2001	USA	prospective	529		13
245	ann surg oncol	SHIVERS	2002	USA	prospective	965		4
246	breast ca res	TSUGAWA	2000	Japan	prospective	48	48	5
248	world j surg	D'EREDITA	2003	Italy	prospective	115	109	5.9
249	j exp clin cancer	D'EREDITA	2001	Italy	prospective	80	80	3.8
250	j am coll surg	O'HEA	1998	USA	prospective	60	59	5

APPENDIX 15: SENTINEL LYMPH NODE BIOPSY EVALUATION: CASE REPORT FORM

M RN: _____ ***Date of Birth:*** / / (YY/MM/DD)

ETHNIC BACKGROUND: _____

- ☐ **CAUCASIAN**
- ☐ **HISPANIC**
- ☐ **ASIAN**
- ☐ **AFRICAN AMERICAN**
- ☐ **INUIT**
- ☐ **OTHER: SPECIFY**_____

MEDICAL HISTORY UNRELATED TO BREAST:

Medical Condition: Year Management:

_____ _____

_____ _____

MEDICAL HISTORY RELATED TO BREAST:

Medical Condition: Year Management:

_____ _____

_____

BREAST BIOPSY HISTOLOGICAL ASSESSMENT:

DATE OF BIOPSY: ___/___/___ (YY/MM/DD)

TYPE OF BIOPSY: _____

HISTOLOGIC DIAGNOSIS:

- ☐ **DCIS**
- ☐ **Infiltrating Ductal Ca**
- ☐ **DCIS + Infiltrating Ductal Ca**
- ☐ **LCIS + Lobular Invasive Focally**

SENTINEL LYMPH NODE BIOPSY

1ST LYMPHOSCINTIGRAPHY

Date of 1st injection ___/___/___ **(YY/MM/DD)**

Tracer 1st injection _____ MicroCi _____

Hours of SLN detection after injection _____

Counts / 10 sec. _____

Intra-mammary lymph node detection _____

2ND LYMPHOSCINTIGRAPHY

Date of 2nd injection / Surgery: ___/___/___ **(YY/MM/DD)**

Tracer 2nd injection _____ MICROCi _____

Hours of SLN detection (SURGERY) after injection _____

Preoperative Counts / 10 sec. _____

Intraoperative counts _____

SENTINEL & AXILLARY LYMPH NODE BIOPSY - HISTOLOGICAL ASSESSMENT:

NUMBER OF SLN EXCISED _____

SLN PATHOLOGY: _____

NUMBER OF AXILLARY NODES EXCISED _____

AXILLARY LN PATHOLOGY _____

TUMOUR PATHOLOGY

TYPE OF LESION _____

SIZE OF LESION (mm) _____

GRADE _____

QUADRANT _____

COMPLEMENTARY TUMOUR _____