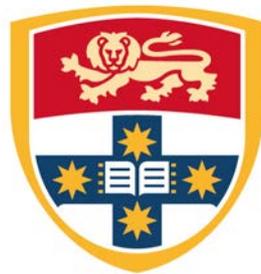


**The Significance of Internal Mammary Lymph Nodes in  
Breast Cancer**

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**A thesis submitted in fulfilment of the requirements for the degree of  
Doctor of Philosophy**

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**Statement of authentication:**

This thesis is submitted to the University of Sydney in fulfilment of the requirement for the degree of Doctor of Philosophy.

The work presented in this thesis is, to the best of my knowledge and belief, original except as acknowledged in the text. I hereby declare that I have not submitted this material, either in full or in part, for a degree at this or any other institution.



Signed:

Date: 30/9/2015

## ABSTRACT

The relevance of assessment and treatment of internal mammary nodes (IMN) in breast cancer has been controversial for a long time. IMN metastasis in breast cancer is a well-documented prognostic factor, of similar importance to axillary lymph node status. Although randomized controlled trials in the 1970s failed to show a survival benefit of the dissection of these nodes during extended radical mastectomy (a procedure that included IMN dissection) they did demonstrate diminished survival of patients with IMN metastasis [1] [2]. Survival is roughly twice as bad in cases with both IMN and axillary node (AN) positivity compared to either alone. Since the demise of extended radical mastectomy many surgeons have lost interest in treating IMNs. However with the advent of sentinel lymph node biopsy (SLNB) utilising peri-tumoural injections, extra-axillary SLN sites have been regularly identified. Even though it may be technically challenging at times to successfully retrieve IMN SNs, the IMN nodes are the commonest sites of extra-axillary SLNs. The rates of identification of IMN SNs varies widely between centres around the world as there are technical differences that impact on the ability to demonstrate them with the different techniques of lymphatic mapping by way of the injection substrate (radioactive colloid) and the injection site (peri-tumoural, subareolar, dermal and others). This has led to many concluding that IMN SLNB is irrelevant. However, the rates of positive of IMN SLNs are significant in most series irrespective of the rate of identification. Irrespective of this controversy, the sceptics question of the value of IMN biopsy in the era of earlier breast cancer diagnosis, when most decisions on systemic therapy are increasingly made on primary tumour characteristics and more often with increasing availability with the addition of genetic expression profiling (GEP). However the results of regional radiotherapy trial (NCIC-CTG MA.20, EORTC 22922–10925 and DBCG-IMN trials) [3-5] has rekindled the interest and highlighted the significance of staging and treatment of IMN metastasis.

In this thesis we explore the literature and controversies surrounding IMN evaluation in breast cancer. From this analysis we determine that IMN staging is inadequate principally due to the variation in breast lymphoscintigraphy technique. According to the literature some lymphoscintigraphy techniques results in very little lymphatic drainage to the IMNs, which in turn could result in under-staging and insufficient treatment of some patients. We also explore the variation in surgical success at retrieving the correct sentinel node in centres where IMN nodes are regularly identified.

Initially a review of the literature and synthesis of ideas surrounding IMN and their role in breast cancer was done to generate hypotheses to be explored in the remainder of the thesis.

The first original study in the thesis investigated the significance of breast lymphoscintigraphy in determining both the status of IMN and AN lymphatic drainage. This study would test the hypothesis that 2 commonly utilised breast lymphoscintigraphy techniques (sub-areolar versus peri-tumoural) would identify the same regional lymph nodes. It is commonly believed that all lymphoscintigraphy techniques identify the same sentinel lymph nodes (SLN) draining the breast. Hybrid imaging technology (SPECT/CT) allows for accurate identification of the exact location of SLNs. Using SPECT/CT, sub-areolar (SA) and peritumoural (PT) lymphoscintigraphy techniques were compared in the same patient on different days whilst the tumour was still in situ. In this multi-centre clinical trial 39 patients sequentially underwent lymphoscintigraphy (SA followed by PT) separated by 2-7 days. Patients were referred by 4 surgeons to 3 lymphoscintigraphy centres, with standardization of isotope ( $^{99m}\text{Tc}$ -antimony sulfide colloid), lymphoscintigraphy and SPECT-CT evaluation techniques. Lymphoscintigraphies were evaluated for SLN concordance and degree of discordance in the AN and IMN. 39 eligible patients, median age 62 years, were recruited.

The results demonstrated successful axillary SLN mapping for SA and PT injection techniques was 87% and 95% respectively. Successful internal mammary SLN mapping occurred with SA and PT lymphoscintigraphy in 5% and 36% respectively. Discordance was identified in the IMN (39%) and AN (21%), with an overall rate of discordance between SA and PT lymphoscintigraphy of 56%. In conclusion there was a high level of discordance demonstrated in the localization of SLN by these commonly used lymphoscintigraphy injection techniques, particularly with IMNs. The majority of IMN discordance was a result of no visualisation of any lymphatic drainage from SA lymphoscintigraphy. This would reflect all superficial lymphoscintigraphy techniques and would have implications for accuracy of AN and particularly IMN staging, which in turn could impact on patient outcome.

The next 2 papers investigate a novel technique of using a large population database and a major centres lymphatic mapping database to determine by mathematical models and algorithms the status of IMN metastasis and its survival implications in early breast cancer.

In the first paper, models were created to estimate the current rate of AN and IM sentinel node metastasis. Data from historical extended radical mastectomy series were analysed to project contemporary rates of IMN metastasis. This information was coupled with derived models and contemporary datasets: a single-institution breast lymphoscintigraphy database (1992-2007) to establish lymphatic anatomy; and the Surveillance, Epidemiology and End-Results (SEER) registries in the US (2000-2003). From this analysis the rates of IMN metastasis and positive sentinel nodes were estimated and models derived to assist with predicting IMN status in patients. If high definition peri-tumoural lymphatic mapping were available, then the predicted rates of positive sentinel nodes in the AN and IMN would be equal. However if information from breast lymphoscintigraphy was deemed sub-optimal and inadequate, predictive tools were outlined to determine the status of IMNs given tumour pathology, AN status and tumour position within the breast. The overall rate of IMN metastasis was estimated approximately 37% the rate of AN metastasis and this would vary given information on tumour position and primary tumour characteristics.

In the final paper further mathematical models were created to quantify the impact on survival of IMN metastases at different tumour and axillary stages. Models were constructed to estimate the survival of patients with and without IMN metastasis. It was assumed that the different rate of survival between medial and lateral sector breast cancers was a result of the differential rate of unrecognized IMN metastases with resultant under-staging and under treatment. The models were then applied to a retrospective database analysis from the Surveillance, Epidemiology and End-Results (SEER) registries from 1994 to 2003. The results demonstrated the 10-year odds of death (OOD) from breast cancer for patients with medial compared with lateral sector tumours ranged from 1.2 to 1.5 depending on stage. The predicted odds of breast cancer death for patients with unrecognized IMN metastases ranged from 2.4 to 20, with the highest OOD in the groups with small tumours with no AN metastasis.

In conclusion this thesis demonstrates the importance of breast lymphoscintigraphy in determining IMN staging in early breast cancer. The peri-tumoural lymphoscintigraphy technique is essential to demonstrate IMN lymphatic drainage that would then guide surgical staging. Mathematical modelling and nomograms have been created to predict the IMN status particularly in situations where breast lymphoscintigraphy has been sub-optimal. Finally mathematical modelling based on a large and robust lymphoscintigraphy database and a large population database has further been able to predict and quantify the significantly worse survival outcomes for patients with undiagnosed IMN metastasis.

# **PRESENTATION OF THESIS**

## **Chapter 1: Introduction to thesis and literature review**

### **Chapter 2 - Publication 1: High-resolution lymphoscintigraphy is essential for recognition of the significance of internal mammary nodes in breast cancer. (Conjoint lead author with A/Prof Andrew J Spillane)**

This study reviews the literature surrounding breast lymphoscintigraphy, internal mammary sentinel node biopsy, IMN metastasis, survival and related changes to adjuvant therapy. In addition an analysis of 2 different nuclear medicine centre lymphoscintigraphy databases are performed demonstrating high rates of IMN drainage and concordance.

### **Chapter 3 – Publication 2: High discordance rates between sub-areolar and peri-tumoural breast lymphoscintigraphy**

This study was designed to evaluate the discrepancy that may exist between 2 different techniques of breast lymphoscintigraphy. To date there has not been a study that directly compares the exact anatomical location of SLNs with different lymphoscintigraphy injection techniques in the same patient using SPECT/CT technology. SPECT/CT technology provides high degree of accuracy in determining the exact location of sentinel lymph nodes compared to the surrounding anatomy. Hence this tool would allow for accurate comparisons of 2 very different techniques of breast lymphoscintigraphy and challenge the old dogma that the entire breast drains as a single ectodermal unit, hence all techniques of lymphoscintigraphy would identify the same lymph nodes. This study was a proof of principle to confirm that discordant outcomes in lymphoscintigraphy techniques do exist not only in determining the internal mammary sentinel nodes but also axillary sentinel nodes.

### **Chapter 4 – Publication 3: Internal mammary node metastasis in breast cancer: Predictive models to determine status & management algorithms.**

This study further reviews IMN evaluation and breast lymphoscintigraphy. Mathematical modelling was created to analyse a large breast cancer database registry in the USA (SEER database) and a large breast lymphoscintigraphy database in Sydney Australia. Data from these 2 databases were pooled together using mathematical modelling to create predictive models. The following was achieved in the study:

1. Predictive models were created to determine the rate of IMN metastasis given the tumour location, size and axillary lymph node status.
2. Predictive models were created that could be coupled with existing breast nomograms (MSKCC sentinel node nomogram) to predict IMN status based on the primary tumour characteristics, tumour position with or without peri-tumoural breast lymphoscintigraphy.
3. Predictive models can be readily utilized to tailor adjuvant radiotherapy to IMNs given inadequacy of breast lymphoscintigraphy and IMN biopsy.

### **Chapter 5 – Publication 4: Internal mammary lymph node metastasis in breast cancer: Predictive models to assist with prognostic influence.**

In this study mathematical models created in chapter 4 were further expanded to determine the diminished survival of patients with untreated IMN metastasis. These models were

applied to a large breast cancer database in the USA (SEER database) and survival differences determined in patients with occult IMN metastasis.

This study highlighted significant diminished survival in breast cancer patients with IMN metastasis that could be amenable to regional radiotherapy.

## **Chapter 6: Summary and conclusions**

## PUBLICATIONS

### Thesis Publications:

- High discordance rates between sub-areolar and peri-tumoural breast lymphoscintigraphy. Eur J Surg Oncol. 2013 Oct; Noushi F, Spillane AJ, Uren RF, Cooper R, Allwright S, Snook KL, Gillet D, Pearce AM, GebSKI V.
- Internal mammary node metastasis in breast cancer: predictive models to assist with prognostic influence. The Breast Epub: 12 Feb 2011; Noushi F, Spillane AJ, Uren R, GebSKI V.
- Internal mammary node metastasis in breast cancer: predictive models to determine status & management algorithms. European Journal of Surgical Oncology 2010 Vol. 36, 16-22; Noushi F, Spillane AJ, Uren R, GebSKI V.
- High resolution lymphoscintigraphy is essential for recognition of the significance of internal mammary nodes in breast cancer. A Spillane, F Noushi (Conjoint lead Author with AJS), R Cooper, V GebSKI, R Uren. Annals of Oncology Vol. 20 (6), 977-84

### Other related publications:

- In regard to Hindie et al.; Int J Radiat Oncol Biol Phys. 2012 Oct; Noushi F, Spillane AJ, Uren RF.
- SPECT/CT scans allow precise anatomical location of sentinel lymph nodes in breast cancer and redefine lymphatic drainage from the breast to the axilla.. Breast. 2012 Aug; Uren R F, Howman-Giles R, Chung DK, Spillane AJ, Noushi F, Gillett D, Gluch L, Mak C, West R, Briody J, Carmalt H.

## GRANTS & AWARDS

- |      |   |
|------|---|
| 2009 | <b>Research Grants:</b><br>National Breast Cancer Foundation – Novel Concept Award/ Pilot Study Grant<br>Friends of the Mater Research Grant<br>Australasian Research Institute Research Grant<br>Novartis Research Grant<br><br>John Collins Gold Medal, Australia New Zealand Breast Cancer Trials Group (ANZBCTG)<br><br>ANZBCTG Travel Grant to present research at their Annual Scientific Meeting |
| 2008 | “Friends of the Mater” Travel Grant to present research results at the Miami Breast Cancer Conference   |

Cancer Institute NSW Travel Grant to present research results at European Society of Surgical Oncology, September 2008

Awarded one of the best research submissions to the 14th ESSO Congress held in The Hague from September 2008

2007 Cancer Institute NSW Clinical and Research Fellowship

## **CONFERENCE PRESENTATIONS**

### **Oral Presentations**

- 2012 Peritumoural versus Subareolar Lymphoscintigraphy – is there a difference? Presentation at Annual Scientific Meeting RACS, Kuala Lumpur
- 2009 Clinical trial to examine the concordance of different breast sentinel node mapping techniques – Annual Scientific Meeting ANZ Breast Cancer Trials Group, July 2009
- 2008 Survival modelling of internal mammary metastasis in breast cancer – Annual Scientific Meeting ANZ Breast Cancer Trials Group, November 2008
- 2008 Non-axillary sentinel nodes in breast cancer, do they matter? Leura VI International Breast Cancer Conference, Sydney September 2008
- 2008 Internal mammary lymph node metastasis in breast cancer: Predictive modelling on the frequency and survival outcomes. 14<sup>th</sup> Congress of European Society of Surgical Oncology, The Hague, Netherlands September 2008. Awarded one of the best presentations of ESSO.
- 2008 Internal Mammary Sentinel Lymph Node in Breast Cancer - Evaluation of a single institution experience and predictive analysis of survival outcomes. 6th Biennial International Sentinel Node Society Meeting in February 2008
- 2008 Internal Mammary Sentinel Lymph Nodes in Breast Cancer. Do they matter? 6th Biennial International Sentinel Node Society Meeting in February 2008
- 2007 Internal Mammary Sentinel Lymphadenectomy Trial Proposal Breast Surgeons NSW Meeting

### **Poster Presentations**

- 2011 Sequential peri-areolar and peri-tumoural SPECT/CT lymphoscintigraphy has identified high rates of discordance in both axillary and internal mammary sentinel lymph node mapping. Presentation at 34<sup>th</sup> Annual San Antonio Breast Cancer Symposium Dec 2011. Noushi F, Spillane AJ, Uren RF, Cooper R, Allwright S, Snook KL, Gillet D, Pearce AM, GebSKI V.
- 2009 Predictive models to estimate the frequency of internal mammary node metastasis and survival impact if untreated. 26<sup>th</sup> Annual Miami Breast Cancer Conference. F Noushi, AJ Spillane, R Uren, V GebSKI

- 2009 High false negative rates in internal mammary node evaluation. 26<sup>th</sup> Annual Miami Breast Cancer Conference. F Noushi, AJ Spillane, R Uren, V Gebski
- 2008 The anatomically correct incidence of internal mammary drainage on lymphoscintigraphy. 31<sup>st</sup> Annual San Antonio Breast Cancer Symposium. AJ Spillane, F Noushi, R Cooper, R Uren.
- 2008 6th Biennial International Sentinel Node Society Meeting in February 2008. Minimal Access Breast Surgery – A single breast incision for breast conservation surgery and sentinel lymph node biopsy. M Brennan, F Noushi, A Spillane

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# **CHAPTER 1: INTRODUCTION TO THESIS AND LITERATURE REVIEW**

In this chapter a literature review will be provided and an introduction to the flow of thesis.

Breast cancer is a leading cause of cancer-related deaths in women today. In the recent decades breast cancer treatment has gradually shifted away from aggressive surgical treatment to less invasive procedures. The treatment for breast cancer has advanced considerably during the last two decades. Survival improvements have come about as a consequence of an increased understanding of the biology of breast cancer, earlier detection, improved staging and refinement of adjuvant systemic therapy including adjuvant endocrine therapy, cytotoxic chemotherapy and other targeted therapies such as Her2 directed Herceptin.

There are several patient and tumour specific factors that impact breast cancer prognosis and in turn the choice to recommend adjuvant therapies. These factors include tumour size, grade, lymph node status, lympho-vascular invasion, oestrogen, progesterone and Her2 status and the patient age. Early prognostic tools from the 1980s, such as the Nottingham Prognostic Index [6], formalised decision-making around systemic adjuvant therapy by using differential weighting of these prognostic factors in a mathematical formula. Later, several online predictive tools became available, such as Adjuvant Online in 1996 [7], to calculate prognosis and quantify benefit from chemo and endocrine therapy. More recently genetic expression profiling (GEP) tools, such as Oncotype DX™, PAM50, EndoPredict and MammaPrint, have developed to assist in prognostication and adjuvant therapy decisions and are increasingly used around the world. Even though these GEP tools are not currently funded in Australia they are likely to be so in the near future.

Despite all this, the regional lymph node evaluation is still considered as one of the most important prognosticators for patients with early breast cancer and the lymph node status is important in the decision algorithm for administration of systemic adjuvant therapies and for loco-regional radiotherapy extent.

### **Breast Cancer Theories:**

For decades there has been debate regarding the theory of breast cancer spread and accordingly the appropriate treatments.

In the early 1900's William Halsted formulated the 'Halsteadian theory' that a tumour grows and metastasizes through lymphatic channels to regional lymph nodes before haematogenous dissemination. Halsted argued that breast cancer would be curable if the tumour and regional nodes were excised in a timely manner. Since then regional lymph node dissection has been an integral part of breast cancer treatment. In accordance with Halsted's principles, breast cancer was treated in a radical manner with removal of the breast, pectoral muscles, axillary and internal mammary lymph nodes.

However, the observation that many patients with breast cancer still relapsed even though the primary cancer was well controlled by local aggressive therapy according to Halsteadian principles [8]. Treatment failure was thought to be a result of early haematogenous dissemination of the tumour rather than an insufficiently radical surgery. From these observations arose the 'Systemic theory' of breast cancer promulgated by Dr Bernard Fisher [9, 10]. He argued that breast cancer is a dualistic phenomenon where the cancer either has or lacks the potential to metastasize. Metastatic potential was realised at the onset with the cancer being a systemic disease requiring systemic therapy. Instead local therapy was important to reduce the likelihood of complications at the primary tumour site and variations in local therapy were unlikely to have a major impact on breast cancer survival. This was demonstrated in the long-term follow-up of the NSABP-B04 and B06 trials [11, 12]. He

further argued that the patient's overall survival was a result of distant disease and systemic therapy would only be effective in showing substantial improvements in overall survival.

However with greater understanding of tumour biology the 'Spectrum theory' evolved, which essentially bridges the two different theories into a single one. This theory initially promulgated by Dr Samuel Hellman, argued that breast cancer is a heterogeneous disease with there being an initial time during tumour growth and maturation where the cancer cells have not metastasized to a distant site [13]. This time point is variable and in some cancers may never come to fruition. Theoretically if local therapy is initiated before this time point is reached then potentially the cancer has been cured and the necessity for systemic therapy is avoided.

No doubt the development and propagation of breast cancer cells and the validity of the above theories would be the result of the interplay between tumour genetic factors, environmental factors and the immune system. These factors would determine the early spread of cancer through the lymphatic and/or vascular system and the effectiveness of loco-regional therapies. Just as GEP tools are available today to assist with adjuvant chemotherapy planning, similarly GEP will become an adjunct to pathological grading and good quality lymphoscintigraphy demonstrating the local lymphatic anatomy should be important in planning regional radiotherapy and surgery. One could postulate that certain GEPs could account for the early vascular dissemination of cancer as in the Systemic theory. Other GEPs would align with the Halsteadian theory of step-wise lymphatic spread that would respond better loco-regional therapies if identified early. Further research is currently underway on GEPs for radiosensitivity of tumours [14, 15] [16]. This will allow us to fine tune the predictive tools to identify the subsets of patients with the greatest potential gain and appropriately tailor loco-regional surgery to those who are likely to not benefit from adjuvant radiotherapy.

Ultimately this would lead to predictive tools, nomograms and algorithms that could assist patients and their physicians to individually tailor breast cancer therapies and reduce the financial, medical and emotional costs associated with unnecessary over treatment that is likely today.

#### **Markers to determine the systemic metastatic potential of breast cancers:**

Failure of local therapy is most notable if the tumour has spread beyond the breast to regional nodes or distant organs. As such the emphasis of neo-adjuvant therapies for advanced breast cancers come into play. To determine cancer spread one needs to evaluate the breast and regional nodes for local spread and the body for distant metastasis. Systemic spread may be evident without regional disease if cancer spread is directly through the vascular system.

#### **Distant metastatic screening:**

Traditionally, systemic imaging to detect the spread of early breast cancer has not been advocated. Arguments for this have included the low sensitivity particularly for low volume metastasis, false positive findings and the associated emotional and financial costs.

However systemic metastatic screening is an underutilised utility that needs further consideration. As imaging modalities become more refined particularly with the advent of PET/CT imaging, the early detection of systemic spread can influence the sequence and extent of oncology therapy (i.e upfront chemotherapy) and potentially reduce cost of unnecessary adjuvant therapies in the event a patient is free of metastasis. However, to date PET / CT technology has been too insensitive to provide adequate reassurance of the absence of systemic disease. Circulating tumour cells and circulating DNA assessment is an area of ongoing research aiming at detecting who has systemic spread and who needs systemic therapy. They are also being investigated for detection of relapse [17].

## **The evolution and significance of regional lymph node evaluation in breast cancer & Sentinel Lymph Node Biopsy (SLNB):**

Historically with the evolution of Halstedian theory, the importance of lymphatic spread has been over emphasized. It is now evident that cancer spread can be through direct haematogenous spread. However, due to cancer heterogeneity, it is yet to be determined the exact sequence of cancer spread that may occur depending on tumour biology, environmental factors and host immunity. Until this can be established, regional node evaluation continues to play an important role in tailoring breast cancer treatment.

Traditionally a complete axillary lymph node dissection (ALND) had been the mainstay to stage and treat the axillary lymph nodes in breast cancer. This led to significant morbidity in many patients particularly when regional metastatic disease was not evident in a large proportion of early breast cancer patients. Yet the importance of determining regional lymph node metastasis continues to be important to firstly allow for accurate tumour staging, which in turn allows for tailoring adjuvant therapies and prognostication of disease. Finally potentially untreated regional disease may impact on patient survival as is evident from some of the radiation trials and meta-analyses [4, 5] [18].

Sentinel lymph node biopsy (SLNB) was developed to minimise the unnecessary surgery and associated morbidity of ALND in patients. This technique is based on the theory that the 'sentinel' node(s) is the first lymph node that drains the lymphatic from the primary breast cancer. The theory assumes that if the sentinel node were pathologically clear of metastatic spread, then all the other regional nodes would also be clear of any metastasis.

In 1993 Krag and colleagues were first to describe the SN biopsy technique in breast cancer [19]. He injected a radioactive tracer around the tumour and the sentinel lymph node was localized during surgery by measuring the radioactivity with a gamma probe. Earlier to this the concept was being evaluated based on the intra-dermal blue dye injection technique by Morton for Melanoma. Around the same time Giuliano translated Morton's melanoma work to breast cancer and introduced a peri-tumoural injection technique with blue dye [20, 21].

SLNB allows for the minimal harvest of regional lymph nodes to determine cancer staging and facilitate further treatment. It is primarily indicated in patients with clinical and radiologically normal axilla. For over 2 decades it has been shown to be safe and effective in detecting axillary nodal metastasis and avoiding unnecessary ALND without compromising patient care. The reported false negativity of this procedure for ANs is in the range of 5%-10% [22]. SNB is now the standard of care for axillary staging. Despite this, there is little consensus on the standardisation of the technique in terms of tracer type and injection location within the breast.

Several different lymphoscintigraphy injection techniques are now in use, with claims that they all identify the same SLNs [23-25]. These broadly include two groups; superficial (periareolar, subareolar, intradermal and subdermal) and deep (peritumoral and intratumoral) injection techniques of tracer within the breast have been reported. Similarly the substrate used for the injection is also varied. Most centres use a combination of a blue dye and radioactive tracer. The combined radioisotope and blue dye method reportedly increases the accuracy of sentinel lymph node detection and decreases the false negativity rate. Patent blue, isosulfan blue, and methylene blue are the agents used as blue dyes. On the other hand, technetium labelled sulfur colloid and albumin are utilized as radioactive substrates.

The lack of consensus on injection technique has arisen from historical studies claiming that the breast to be a single ectodermal unit draining to the antero-pectoral axillary lymph nodes, and that lymphatics from the parenchyma join with those from the areola and drain to a

common node. However recently both anatomical and clinical studies have clearly demonstrated the contention that all methods of lymphoscintigraphy to map to the same anterior pectoral axillary SLN to be incorrect [26-28]. In addition there is a great disparity in the reported rates of IMN identification. This in itself would place into question the accuracy of the technique in identifying the same axillary sentinel nodes. The gold standard technique of breast lymphoscintigraphy has not been established as direct comparisons were not accurately done.

With the recent advent of hybrid imaging with SPECT/CT technology the anatomical location of SLN has been greatly enhanced [29]. Exact locations of lymph nodes can be determined with relation to surrounding anatomical landmarks. Direct comparisons of different lymphoscintigraphy techniques can be performed with a high level of accuracy rather than the reliance on conventional planar lymphoscintigraphy imaging and adjuncts such as intra-operative blue-dye injections.

This information correlates well to the historical and more recent cadaveric work on the location of IMN nodes particularly [26-28] [30]. A 2001 review on the historical cadaveric studies and IM sentinel node dissection technique was well presented by Veronesi et al [30]. These studies determine that the number of IMN range from 4-8 and are principally located in the first 3 intercostal spaces in close proximity to the internal mammary vessels in the extra-pleural space. The nodes can be successfully retrieved through the anterior trans-pectoral approach as described by Veronosi et al [30].

To date there has not been a study that directly compares the exact anatomical location of SLNs with different lymphoscintigraphy injection techniques in the same patient using SPECT/ CT technology. The aim of the study in **chapter 3** was to test the hypothesis that sub-areolar lymphoscintigraphy identifies the same SLN as peri-tumoural injections, both in the axilla and non-axillary lymph nodes. This study was a proof of principle to confirm that discordant outcomes in lymphoscintigraphy techniques do exist particularly in determining the IMN metastasis but also importantly for the axilla.

A recent meta-analysis of thirteen sentinel lymph node trials that addressed the different lymphoscintigraphy techniques, concluded that although all injection techniques had a similar high rate of AN identification, the rates of IMN identification was the highest in trials with deeper tracer injections [31]. In addition, despite the paucity of good trial data, this analysis also concluded from 6 trials that there was a significant rate of sentinel node discordance in axilla (4-73%) and IMNs (0-61%) between the different injection techniques. Our study presented in this meta-analysis was the only trial that had analysed two different lymphoscintigraphy injection sites administered sequentially in the same patient with the superior accuracy of SPECT/CT technology to clearly identify the position of sentinel nodes. Other trials had confounding variables such as:

1. Non-sequential tracer injections in different patient groups [32-34]
2. Rapid sequence of sequential radioactive tracer administration, which did not allow tracer to wash out between different injection site comparisons [32] [35]
3. Sequential lymphoscintigraphy of differing tracer substance (blue dye versus radioisotope and different radioisotope) [35-37]
4. All studies utilised conventional planar lymphoscintigraphy imaging techniques [32, 33, 35-38], which lacked the accuracy of SPECT/CT.

Despite these confounding variables, discordance in both the axillary and IMN sentinel nodes identification were confirmed. However the clinical significance of high discordance rates has not been addressed adequately by any of these studies. Low axillary false-negative rates (5-10%) were established in three trials on subsequent ALND [32, 34, 35]. However the overall clinical impact of the high lymphoscintigraphy discordance rates may realistically only affect

a few patients as only one-third of patients will have axillary metastasis and other surgical factors such as utilisation of blue dye, partial lymphoscintigraphy concordance and excision of palpable and additional non-sentinel nodes would reduce the overall false negative rate.

Despite a reported false negative rate for axillary staging of 5-10%, SLNB has significantly reduced by 10-30% all morbidities that were observed after ALND. This included seroma and hematoma formation, paresthesia, pain, lymphoedema, restricted arm and shoulder function. This was demonstrated particularly well in a SNAC trial with morbidity of ALND demonstrated well into the long-term [39]. To that end SLNB has served its purpose well. However as evidenced from the recent meta-analysis, extra-axillary sentinel node staging has been widely variable depending on the techniques used. Superficial lymphoscintigraphy injection techniques ignores the fact that the breast is a three dimensional structure with both superficial and deep lymphatic channels draining into different nodes, detailed below and picture 1 [26-28].

Hence the significance of accurate breast staging with lymphoscintigraphy may be most relevant in relation to extra-axillary regional nodes, such as IMNs. Here the surgical access is difficult for the majority of breast surgeons and one cannot simply palpate for abnormal nodes or simply sample a few extra lymph nodes as it is often done with the ANs to improve on the positive node count and reduce false negativity.

#### **Relevance of IMN metastasis in breast cancer:**

Internal mammary lymph node (IMN) metastasis in breast cancer is a well-documented prognostic factor, of similar importance to axillary-lymph-node status. Although randomized controlled trials in the 1970s failed to show a survival benefit of the dissection of these nodes during extended radical mastectomy (ERM), a procedure that included IMN dissection, they did demonstrate diminished survival of patients with IMN metastasis [1, 2]. However these trials did identify those patients who demonstrated both IMN and AN metastasis had a significant reduction in their overall survival compared to either nodal group being positive alone. In fact their survival rates were reduced by more than half if both nodal groups were involved in the historic ERM trials. In these trials the annual death rates increased from 5.5% and 7.7% for IMN+ and AN+ patients respectively to 16.3% for patients with both AN+ and IMN+ [1]. More recent epidemiological series have shown worse survival of patients with medial compared to lateral quadrant tumours [40-45]. All these studies concluded that a greater percentage of undiagnosed IMN metastasis and as a result under-staging of these patients was responsible for the poorer survival and not inherently different tumour biology of medial tumours. Other sources of evidence have been retrospective analysis of large lymphoscintigraphy databases. Two studies demonstrated that IMN drainage on lymphoscintigraphy conferred a worse prognosis [46, 47].

Since the demise of extended radical mastectomy many surgeons and oncologists had lost interest in treating IMNs. They questioned the value of IMN biopsy in the era of earlier breast cancer diagnosis, when most decisions on systemic therapy are increasingly made on primary tumour characteristics and genomic profiling. However the Milan experience with routine biopsy of IMNs and targeted radiation of the IMNs if metastasis were demonstrated had shown better than predicted 5-year survival of patients with IMN metastasis. This publication has suggested the significance of targeted therapy for IMN metastasis in improving survival outcomes comparable to those without IMN metastasis [48].

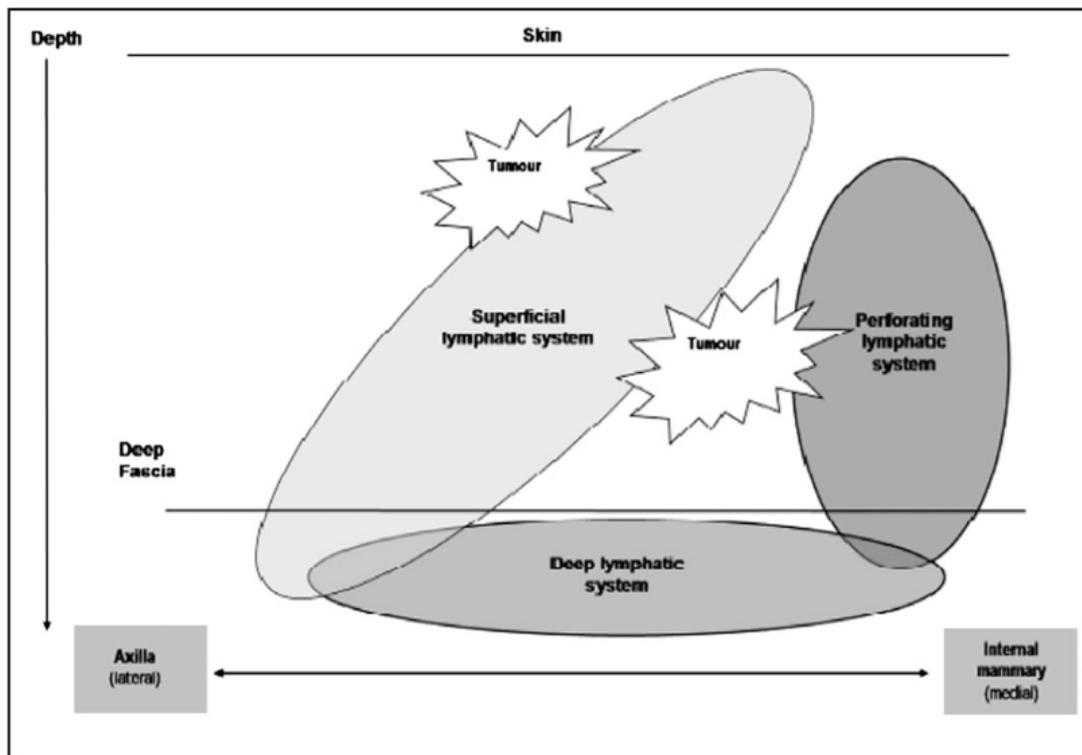
Moreover evidence supporting the appropriate management of IMN metastasis has been demonstrated by the results of the recent regional radiotherapy trial results (NCIC-CTG MA.20, EORTC 22922-10925 and DBCG-IMN trials) [3-5], detailed below. These landmark trials have rekindled the importance of IMN staging and treatment as they have demonstrated

the success of regional therapy, particularly IMN, in improving disease free survival and overall survival in 2 of the 3 trials.

### Challenges in accurate lymphatic mapping of IMN drainage:

With the advent of sentinel node lymphatic mapping, this had rekindled interest the status of IMNs. Deeper lymphoscintigraphy techniques visualised IMN more frequently, as detailed above. High rates of IMN mapping success have been attributed to ultrasound-guided peritumoural injection with  $^{99m}\text{Tc}$ -antimony sulfide colloid radiopharmaceutical [49]. Two important determinants of detection of IMN drainage are the radiocolloid particle size and the site of radiocolloid injection in the breast: deep peritumoural injections require small-particle colloids because large-particle radiocolloids do not migrate well from the injection site. When small-particle radiocolloids are not available, the breast injections have been given superficially into the dermis or in the peri-areolar region, which in the majority of patients only identifies axillary sentinel lymph nodes.

As detailed by recent anatomic studies by Suami et al. and lymphoscintigraphy observations [26-28], superficial sites rarely drain to nodes outside the axilla. These superficial injection techniques ignore the fact that the breast is a 3 dimensional structure and the differing superficial and deep lymphatic systems. Deep peri-tumoural lymphoscintigraphy (draining via the perforating lymphatic system) have a higher rate of IMN drainage than sub-areolar or subdermal (superficial lymphatic system) injections. Also, peri-tumoural injection more accurately demonstrates the true lymphatic drainage of the tumour than an injection given away from the tumour site in the skin or around the areola. Because of these issues, the reported rates of IMN drainage on lymphoscintigraphy vary greatly, from 0 to 38% of all breast tumours.



Picture 1: Model of breast lymphatic anatomy in relation to tumour position in depth and laterality. Modified from Suami et al. [26]

In **chapter 3**, we trial 2 different breast lymphoscintigraphy techniques to determine the difference in rate of IMN drainage and concordance in the sentinel nodes advised in all nodal basins.

### **Challenges in IMN biopsy and false negativity:**

The rate of visualization of sentinel IMN seems to be the principal determinant of whether surgeons are advocates of trans-pectoral IMN biopsy. Infrequent opportunity to do IMN biopsy in most breast surgeons' settings can lead to lack of conviction that it is of value. Many breast surgeons, due to the lack of technical expertise and familiarity with the route of access, have concerns about the rate of complications of the procedure. Infrequent IMN biopsy leads to higher rates of false negativity given the challenging surgical techniques. When IMN SLN is identified the success rate of biopsy is very variable ranging from 45-88%, from centres interested in doing biopsy. So predictably the rates of success in the average breast surgeons practice would be significantly lower.

### **Shifting paradigm – Is radiotherapy becoming the new tool to manage regional metastatic disease?**

There has been greater emphasis placed on regional nodal management by radiotherapy rather than surgery stemming from the results of a number of surgical and radiotherapy trials and meta-analysis. This is explored further:

### **Axillary management in patients with low volume metastasis – outcomes of recent surgical trials:**

Initially an ALND was the mainstay of regional treatment for all breast cancer patients. Due to the significant morbidity associated with this procedure, it was replaced with SLNB. SLNB became the standard of care for all early breast cancer patients. If any metastatic disease was identified in the ANs then a complete axillary clearance was recommended. However the results of two recent surgical trials (American College of Surgeons Oncology Group (ACOSOG) Z0011 trial [50] the IBCSG 23-01 trial [51]) have challenged this notion for micro-metastatic and low volume disease (fewer than 3 axillary metastasis with no extra-nodal spread). The results from these trials demonstrated that ALND could be safely omitted in low volume axillary metastasis. The impact of radiotherapy in these trials managing any residual regional disease has been debated. However the role of targeted regional radiotherapy replacing ALND has been supported by the results of another landmark AMAROS (10981/22023) trial [52].

The Z0011 trial addressed whether SLNB alone resulted in diminished survival in women with early-stage breast cancer. Eligible patients were clinically staged T1-2, clinically node negative, but had 1 or 2 positive sentinel nodes at surgery. Patients with matted lymph nodes and/or gross extra-nodal disease were excluded. Patients undergoing breast conserving surgery and adjuvant radiation therapy were randomized to receive SLNB with or without completion ALND. With a median follow-up of 6.3 years, regional recurrence rates were very low at 0.9% in the SLNB arm alone compared to 0.5% in the ALND group. There were no differences in disease-free survival or overall survival. However it was evident that a significant number of the trial patients had favourable tumour characteristics and early stage. In addition many received other forms of adjuvant therapy particularly radiotherapy, which would have treated their low volume of residual axillary disease. Radiotherapy delivered was either in the form of higher tangential radiation fields treating the lower axilla or direct nodal irradiation [53]. This in fact rendered the trial more a comparison of axillary surgery versus radiotherapy. Arguably the SLNB in itself may have treated a majority of patients with low volume disease. This was evident in the IBCSG 23-01 trial where only 13% of patients were

found to have additional axillary metastasis in the ALND arm of the trial, which would have been similar in the untreated group of patients.

In addition the recently published AMAROS (10981/22023) trial directly addressed the omission of a completion ALND in women with node positive early-stage breast cancer and treatment with axillary radiotherapy [52]. In this study the patients were T1-2, clinically node negative, but diagnosed with a positive SLNB and were randomized to receive ALND or nodal radiation therapy. In contrast to the Z0011 study, however, all patients undergoing nodal radiation received treatment to both the full axilla (I to III) and supraclavicular nodes. The 5-year axillary recurrence rate was also low in both arms with no statistical difference: 0.43% in the ALND group and 1.19% in the axillary radiation therapy group. In addition there were no differences in disease-free survival or overall survival. Interestingly it did demonstrate significantly higher rates of lymphoedema in the surgical group compared to the radiation group (23% vs 11% at 5 years), also detailed below. This supports the contention that regional radiotherapy can adequately treat low volume axillary disease either directly or indirectly through tangential radiation fields.

Both the Z0011 and AMAROS trials had patients with favorable tumor characteristics, in that they were clinically T1-2, N0, fewer than 30% had grade 3 disease, and only 27% and 33%, respectively, had positive non-sentinel lymph nodes. Additionally, 40% of patients in both trials had micrometastatic nodal tumor deposits. As such one cannot generalize the management of the axilla based on these trial given the favorable characteristics and a low burden of axillary disease. In addition not all tumours may be sensitive to the effects of radiotherapy, as such surgery and other adjuvant therapies will still have a role in the management of regional disease. Arguably, radiotherapy having fewer side-effects particularly for the axillary nodal group as demonstrated by the results of the AMAROS trial, would appropriately replace ALND in patients with favourable tumour characteristics and low volume disease.

Although the ‘Systemic theorists’ would argue for minimisation of regional therapy based on the evidence of these surgical trials, however the contradictory outcomes of recent three large radiotherapy trials (European EORTC 22922–10925 [4] and the Danish Breast Cancer Group IMN radiation trial DBCG-IMN[5]) and Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) meta-analysis [18] [54] provide more evidence that regional therapy does impact survival in a significant number of cancer patients.

The outcome of the EBCTCG meta-analysis of post-mastectomy radiation therapy trials [18] demonstrated a reduction in breast cancer recurrence, disease-free survival and overall survival in women with even with one positive lymph node who received comprehensive radiation therapy including the chest wall, supra-clavicular or axillary fossa (or both), and IMN. The loco-regional recurrence rate was 16.5% higher when no radiotherapy was added, with an improvement in breast cancer mortality of 7.9%. For patients with four or more positive nodes, the increased loco-regional recurrence rate was 19.1% higher without radiotherapy, with a reduction in breast cancer mortality of 9.3%. This corroborates their earlier data showing that the reduction in loco-regional recurrence leads to a decreased breast cancer mortality in women with a smaller burden of nodal metastases [54]. Therefore, a reduction in loco-regional recurrence due to local-regional therapies can result in a relatively greater impact on survival.

#### **Management of regional nodes with radiotherapy - outcomes of recent regional and IMN radiation trials:**

NCIC- CTG MA.20 randomized high-risk node-negative patients (10% of the trial population who were defined as those with primary tumour  $\geq 5\text{cm}$  or  $\geq 2\text{cm}$  and  $< 10$  ANs removed with either one of the following: oestrogen receptor negative, grade 3 or lymphovascular invasion

evident) or node-positive breast cancer patients who underwent breast conserving surgery to whole-breast irradiation or whole-breast irradiation and regional lymph node irradiation, which included the internal mammary nodes in the first 3 intercostal spaces, the supraclavicular, and high axillary lymph nodes [3]. Nearly all patients received adjuvant chemotherapy (91%), and the majority received adjuvant endocrine therapy (77%). All node-positive patients underwent ALND. At the 10 year follow-up there was no significant difference in overall survival in the two groups (82.8 versus 81.8%, HR=0.91, P=0.38). However disease free survival was superior in the nodal radiotherapy arm of the study (82% versus 77%, HR=0.76, P=0.01). Arguably with an improved disease free survival from a reduction in distant metastatic rate (by 3.6%) this would result eventually in a overall survival difference with longer follow-up.

The ten-year results from the phase 3 EORTC 22922/10925 trial demonstrated both improvement in disease free and overall survival [4]. In this trial a total of 4004 patients were randomised to either breast/thoracic-wall irradiation alone to breast/thoracic-wall and regional irradiation, which included the internal mammary chain and medial supraclavicular lymph nodes. Eligible patients had pathologically positive axillary lymph nodes or were node-negative with central or medial tumours. More than 90% of patients in each study group underwent partial or total axillary lymph node dissection, and the majority of patients received systemic therapy (83-85%). At the 10-year follow-up, overall survival was marginally improved in the nodal radiotherapy group (82.3% versus 80.7%, HR=0.87, P=0.06) however not significant. However disease free survival was superior in the nodal radiotherapy group (78% versus 75%, HR=0.86, P=0.04) and breast-cancer mortality was lower (12.5% versus 14.4%, HR=0.82, P=0.02).

In the Danish (DBCG) IMN irradiation trial, it was shown that adjuvant radiotherapy to the IMNs improved overall survival (published ESTRO 33 meeting abstract, April 2014) [5]. This prospective study on 3,072 breast cancer patients with lymph node positive disease were treated with standard radiotherapy plus IMN irradiation for right sided cancers, whereas patients with left sided breast cancer did not receive any IMN irradiation, as this could cause radiotherapy-induced damage to the heart. Patients in the two groups were comparable with respect to independent risk factors for breast cancer death and all patients were allocated to adjuvant systemic treatment. Notably in this trial both sided cancers received medial supraclavicular irradiation, so the only variable in the treatment arms were IMN irradiation for right-sided breast cancers. In this trial, after a median follow-up of seven years, overall survival was 78% versus 75% in favour of IMN radiotherapy, (HR=0.86, p=0.04). The number of deaths from cardiac disease was comparable in the two groups, with 9 deaths in the no IMN radiotherapy group and 8 deaths in the IMN radiotherapy group. Death from breast cancer was more frequent in the no IMN radiotherapy group (n=366) than in the IMN radiotherapy group (n=309).

Finally, an underpowered French IMN irradiation trial did not show an overall survival benefit with the use of internal mammary irradiation [55]. However a subgroup analysis of pN0 patients with medial and central tumours showed a non-significant benefit in overall survival. In addition there was a reduction in distant metastatic rate reported, however this did not impact overall survival in the reported follow-up. The authors concluded that the study could not rule out a moderate benefit from IMN irradiation, especially with more modern, conformal techniques applied to a higher risk population.

Notably the radiotherapy trials demonstrate some modest improvement in overall survival in two studies. They all demonstrate significant disease-free survival difference favouring regional radiotherapy. Arguably the reduction in disease recurrence would in the longer-term result in improved overall survival, which may yet eventuate as the trial patients continue to be followed up. It has been demonstrated in the large radiotherapy trial meta-analysis (Early

Breast Cancer Trialists' Collaborative Group) that prevention of breast cancer recurrence does directly impact on overall survival [54].

However of greater importance are the prevention of unnecessary regional therapy and the associated side-effects by proper patient selection that would benefit from this. From these radiation trial results (aside from the Danish trial) one cannot ascertain the extent and significance of different radiation fields (particularly the impact of added medial supraclavicular irradiation versus internal mammary node irradiation) and the tumour biology on the overall outcomes. However the Danish trial does support the notion that the most significant benefit arose from IMN radiation.

Finally all these radiation trials will require longer follow-up to determine the true extent of disease recurrence on survival and the detrimental impact of long-term radiation side effects on survival, as detailed below.

With conflicting trial data results conducted in an era prior to significant improvements in adjuvant endocrine and chemotherapies, it can be difficult to formulate guidelines in the management of regional nodes for oncologists to follow. Moreover with the improvement in the knowledge of GEP of breast cancers that are sensitive to radiation and have a preference to regional spread rather than vascular, radiation therapy and surgery can be appropriately tailored. Until then one would have to aim to eradicate any potential nidus of regional disease either by surgery or radiotherapy.

Regional nodal management with surgery and radiotherapy is well established in patients with a high volume of regional metastasis and low volume or no systemic metastasis. However the crux to appropriate regional node management in early breast cancer patients with no obvious regional disease is accurate lymphoscintigraphy, which is particularly significant for IMN staging mentioned above. As investigated in chapter 3, inaccurate lymphoscintigraphy techniques can lead to discordant staging and potentially missed regional metastasis. In the axilla, the impact of inaccurate lymphoscintigraphy will be negated by the common practise of additional lymph node sampling and the impact of adjuvant therapies such as tangential radiotherapy fields treating the axilla in breast conserving patients. This may have been prevalent in the lower risk patients with low volume axillary disease seen in the surgical trials.

However the impact of missed IMN metastasis would only be relevant in a few patients predictably around 9-12% patients at the time of presentation. Naturally some may be treated by tangential radiotherapy of the breast or other adjuvant therapies. Yet it is only a small number of patients with occult IMN metastasis that continue to suffer poor survival outcomes if left untreated. As proportionally these patients are only a few, yet the magnitude of their diminished survival is sufficient to impact on the overall survival of the entire trial patient cohort. The significance of even a 'marginal' survival improvement with IMN radiotherapy, does reflect a large magnitude of survival improvement that these patients with occult untreated IMN metastasis achieve. Although survival continues to be the principal focus of many trials, there is little research on the untold quality of life impact for the small number of patients that get IMN metastasis with local invasion into the sternum, chest wall and pleural disease. So to dismiss these trial results as insignificant and irrelevant does threaten the adequacy of treatment provided to a small but significant patient cohort with IMN metastasis.

This was evident in the sub-group analyses of the EORTC 22922/10925 trial that demonstrated significant survival differences particularly in patients that were axillary node negative with medial and larger (T2) tumours [4]. In **chapter 5** of this thesis we explore through modelling the significant diminished survival of a few patients with untreated IMN metastasis, which was reflected in the small differences in the overall patient survival for patients with breast cancers locally in the medial versus lateral breast quadrants.

However to tailor regional radiotherapy treatment to avoid overtreatment and unnecessary toxicities can be a challenge particularly for the IMN nodal group. Once again accurate lymphoscintigraphy can be beneficial in determining the likelihood of IMN metastasis, so as to tailor surgical exploration and radiotherapy as discussed in **chapter 4** of this thesis.

### **Toxicity associated with breast cancer radiotherapy:**

Historically significant morbidity and mortality has been documented for collateral damage from breast cancer related radiotherapy and late effects of radiotherapy can begin and progress decades after treatment [56, 57] [58]. These include cardiac disease, pneumonitis, brachial plexopathy, arm/breast lymphoedema, rib fractures, impaired shoulder function and secondary malignancy [59] [58]. Older data from the EBCTCG meta-analysis [60] determined higher non-breast cancer related deaths in irradiated patients (rate risk of 1.12). Although multi-factorial, a significant part of this rate was mainly from heart disease (rate ratio 1.27) and lung cancer (rate ratio 1.78) in irradiated patients. Radiation pneumonitis has also been reported following breast radiation therapy, particularly in patients also receiving adjuvant chemotherapy and regional node radiation. Brachial plexopathy is more difficult to study given it is a very late development with a low incidence. It has been reported following axillary and/or supraclavicular radiation therapy.

Finally lymphoedema from radiation therapy has been somewhat overestimated historically. There is now significant evidence that radiation to the breast and chest wall alone does not result in increased lymphoedema risk, whereas radiation to the regional lymph nodes does. This is most significant after targeted supraclavicular radiotherapy in conjunction with an ALND. Other factors related to increased risk of lymphoedema include BMI and the extent of axillary surgery. A recent prospective study on 1,476 patients [61], demonstrated that targeted radiation to the regional lymph (supraclavicular) nodes has been shown to increase risk of lymphoedema (21.9%), compared with radiation to the breast or chest wall alone (3.1%) and no radiotherapy (3.0%). On multivariate analysis, the addition of supraclavicular radiation significantly increased the lymphoedema risk compared with breast/chest wall radiation alone, with an HR of 1.7. In comparison, the HR for undergoing axillary lymph node dissection was 3.5. Most notable has been the results of the AMAROS trial, where at 5 years patients in the axillary radiotherapy arm had a significantly lower rate of lymphoedema (11% vs 23% at 5 years), however longer term follow-up will determine if this difference continues [52]. Yet one cannot solely attribute locoregional surgery and radiotherapy as the only cause of lymphoedema, as increasing evidence has attributed systemic taxane chemotherapy as a contributing factor in some studies [62].

In the last few decades there has been a significant improvement in the targeted delivery of radiotherapy. With 3D (computed tomography-based) planning, prone delivery of radiotherapy and deep inspiratory breath holding techniques have resulted in improved radiation dose distributions with sparing of the heart and lungs and the reduction of associated toxicities. These improvements have been quantified over the decades from 1973-2008 by an analysis of mortality based on laterality of breast cancer in the SEER database [63]. Yet as we trend to being more liberal with radiation to regional nodal fields, particularly the IMN, there will be a greater emphasis on the accurate quantification of the long term morbidity and mortality of radiation. This will allow one to adequately balance the potential gains versus toxicities between competing modalities of local therapy; surgery versus radiotherapy.

### **Future trends towards tailoring regional radiotherapy:**

As often is the case, lymph node metastasis particularly to the IMNs are not readily visible on standard breast imaging and staging scans. Even to date PET-CT studies have not been

accurate in detecting low volume disease in lymph nodes, particularly small IMNs, however this research is ongoing [64]. Furthermore one could argue different genomic and pathological tumour sub-types may not respond to radiotherapy and require surgical dissection. Research on radiosensitivity genomic signatures may provide us with this answer in the near future [14] [15].

Until such information is available it is may be prudent to offer all breast cancer patients the option of optimal regional treatment with both surgery and radiotherapy, which can potentially impact their survival. However this comes at a risk of overtreatment and the associated morbidity. To avoid this more tools are required to appropriately tailor regional therapies. This is on the horizon with improvement in the imaging modalities, radiosensitivity genomic signatures, new methods of radiotherapy delivery regimens and refinement of surgical evaluation and treatment of regional nodes.

Surgical evaluation and treatment of regional nodes relies heavily on accuracy of SLNB, which has now replaced ALND. Yet this technology has not been accurate in determining IMN metastasis. The principle aim of this thesis is to highlight the importance of regional lymph node evaluation with accurate breast lymphoscintigraphy and evaluation of the often-ignored IMN.

### **Predictive nomograms as a surrogate for accurate breast lymphoscintigraphy and biopsy of IMN SLNs:**

With the resurgence of IMN treatment that has come from the radiation trials, there will be increasing demand for improved surgical evaluation of these nodes. However limitations in access and surgical expertise will remain. This has lead many oncology teams selecting all their patients with any regional lymph node involvement to receive radiotherapy to all regional fields. This trend will result in increase radiotherapy dosage to the heart particularly with left sided tumours and the potential for long-term adverse outcomes [58].

As such predictive nomograms and algorithms may be needed to aid with selective delivery of IMN radiotherapy particularly for left sided breast cancers, which undoubtedly will have the greatest cardiac toxicity.

Numerous nomograms have been created to predict the status of non-sentinel axillary lymph node metastasis after successful diagnosis of sentinel node metastasis. However, aside from the original Memorial Sloan Kettering Cancer Centre (MSKCC) sentinel lymph node metastasis nomogram [65] and an earlier model by Olivotto et al [66], no further work has been done to refine the sentinel node nomogram. No doubt, these nomograms can be further refined with genomic profiling to provide an accurate prediction of the regional nodal status, which in time may replace surgical biopsy for some early breast cancers. The MSKCC nomogram was created to predict the status of axillary sentinel nodes, however they were not designed to predict the status of IMN.

As detailed in **Chapter 4**, one can further improve on this nomogram to factor in tumour position, depth, axillary nodal status and IMN lymphatic drainage to predict the IMN status. This can be done with or without results of accurate peri-tumoural lymphoscintigraphy or even attempt at IMN surgical biopsy. Such nomograms can be a very useful adjunct to tailor regional radiotherapy, particularly for left sided breast cancers.

Furthermore results of these nomograms could be coupled with the outcomes of large radiation trial databases (NCIC-CTG MA.20, EORTC 22922–10925 and DBCG-IMN trials) to determine the impact of IMN radiation on any improved survival outcomes.

## **Thesis Publications:**

**Chapter 2:** High-resolution lymphoscintigraphy is essential for recognition of the significance of internal mammary nodes in breast cancer.

This study reviews the literature surrounding breast lymphoscintigraphy, internal mammary SLNB metastasis, survival and related changes to adjuvant therapy. In addition an analysis of 2 different nuclear medicine centre lymphoscintigraphy databases are performed demonstrating high rates of IMN drainage and concordance.

**Chapter 3:** High discordance rates between sub-areolar and peri-tumoural breast lymphoscintigraphy

This clinical trial was designed to evaluate the discrepancy that may exist between 2 different techniques of breast lymphoscintigraphy. To date there has not been a study that directly compares the exact anatomical location of SLNs with different lymphoscintigraphy injection techniques in the same patient using SPECT/ CT technology. SPECT/CT technology provides high degree of accuracy in determining the exact location of sentinel lymph nodes compared to the surrounding anatomy. Hence this tool would allow for accurate comparisons of 2 very different techniques of breast lymphoscintigraphy and challenge the old dogma that the entire breast drains as a single ectodermal unit, hence all techniques of lymphoscintigraphy would identify the same lymph nodes. This study was a proof of principle to confirm that discordant outcomes in lymphoscintigraphy techniques do exist not only in determining the internal mammary sentinel nodes but also axillary sentinel nodes.

**Chapter 4:** Internal mammary node metastasis in breast cancer: Predictive models to determine status & management algorithms.

This study further reviews IMN evaluation and breast lymphoscintigraphy. Mathematical modelling was created to analyse a large breast cancer database registry in the USA (SEER database) and a large breast lymphoscintigraphy database in Sydney Australia. Data from these 2 databases were pooled together using mathematical modelling to create predictive models. The following was achieved in the study:

1. Predictive models were created to determine the rate of IMN metastasis given the tumour location, size and axillary lymph node status.
2. Predictive models were created that could be coupled with existing breast nomograms (MSKCC sentinel node nomogram) to predict IMN status based on the primary tumour characteristics, tumour position with or without peri-tumoural breast lymphoscintigraphy.
3. Predictive models can be readily utilized to tailor adjuvant radiotherapy to IMNs given inadequacy of breast lymphoscintigraphy and IMN biopsy.

**Chapter 5:** Internal mammary lymph node metastasis in breast cancer: Predictive models to assist with prognostic influence.

In this study mathematical models created in chapter 4 were further expanded to determine the diminished survival of patients with untreated IMN metastasis. These models were applied to a large breast cancer database in the USA (SEER database) and survival differences determined in patients with occult IMN metastasis.

This study highlighted significant diminished survival in breast cancer patients with IMN metastasis that could be amenable to regional radiotherapy.

## **CHAPTER 2:**

**High-resolution lymphoscintigraphy is essential for recognition of the significance of internal mammary nodes in breast cancer.**

# High-resolution lymphoscintigraphy is essential for recognition of the significance of internal mammary nodes in breast cancer

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**Background:** Sentinel node biopsy (SNB) of internal mammary nodes (IMNs) in breast cancer is controversial. Most centers rarely identify IMN on lymphoscintigraphy but others report up to 45% of cases. Controversy relates to the technique of lymphatic mapping, safety of IMN SNB, the significance of positive IMN, and potential to impact survival.

**Methods:** Assessment of drainage rates from two unrelated nuclear medicine departments' databases. Review of related literature.

**Results:** High-resolution lymphoscintigraphy results in IMN drainage in one-third of breast cancers. There is a learning curve for the technique. In 1754 consecutive cases, internal mammary drainage occurred in 53% of medial tumors, 37% midline tumors and 24% of lateral tumors (overall 34%). Extended radical mastectomy series also demonstrate the (approximately) 1/3 ratio when comparing IMN positivity rates to axillary node positivity rates (18.8% : 48.3%) and in node-positive patients (31% : 100%). The management altering potential of IMN assessment and potential survival impact are discussed.

**Conclusions:** IMN mapping gives information that alters management in up to one-third of cases. These rates of IMN drainage are reproducible and reflect lymphatic density and anatomy of the breast. A priority need exists to establish a collaborative clinical trial to clarify the value of IMN assessment.

**Key words:** breast cancer, internal mammary nodes, lymphoscintigraphy, sentinel node biopsy

## introduction

The extended radical mastectomy (ERM) experience from the 1950s until the 1980s has provided compelling evidence that the presence of internal mammary node (IMN) metastasis in breast cancer is a prognostic factor of similar importance to axillary node positivity. The combination of positive nodes in both areas was shown to be indicative of doubly worse prognosis in nearly all these studies [1–16]. These studies were from a time when the concept of adjuvant therapy was in its infancy. In the 1960s, a large prospective, randomized trial of the International Cooperative Group comparing ERM and radical mastectomy demonstrated no statistical difference in overall survival, relapse-free survival or local-regional recurrence between the two treatment groups at 10-year follow-up [11]. The practice of IMN biopsy then largely fell into irrelevance. The issue of anatomical inaccessibility and logistics of IMN biopsy has seen it become a neglected aspect of breast cancer staging and thus have minimal impact on management decisions over the last

20–30 years. More recently, sentinel node biopsy (SNB) has replaced axillary dissection for staging the axilla [17–22]. Depending on the lymphoscintigraphy technique used and the interest of the nuclear medicine physicians (and the surgeons) involved, the advent of SNB and implementation of lymphatic mapping has seen the documentation of a wide variation in rates of IMN drainage on lymphoscintigraphy. This ranges from not doing lymphatic mapping preoperatively and thus 0% to 45% [23–25]. In centers where the lymphoscintigraphy IMN drainage rate is low then it would clearly have very little impact on clinical practice. In comparison, if surgeons and other members of the multidisciplinary team are working in an environment where the rate of IMN drainage is high, where more than one in three patients have IMN drainage, it is difficult to ignore the information forthcoming.

The relevance of IMN is reviewed starting with the lymphatic anatomy of the breast as this is central to question as to what is the true rate of IMN drainage which has implications on clinical relevance. Previous reviews by authors from Memorial Sloan Kettering Cancer Center [26, 27] and more recently by Chen et al. [28] underestimate the likely potential impact of the IMN on breast cancer management.

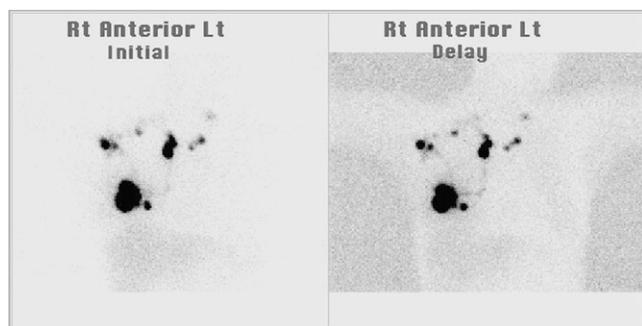
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## technical issues of lymphatic mapping and rates of IMN drainage

High rates of IM mapping success have been attributed to peritumoral injection with technetium antimony sulfide colloid radioisotope [24, 29] (Figure 1). Review of the available literature indicates that this technical explanation is over simplified. It is clear that superficial injections into the subareolar area or dermis over the tumor have a very low chance of showing IMN drainage [25, 30]. However, even in nuclear medicine facilities that use peritumoral injections, there is still a very wide range of drainage rates (see Table 1). This is also the case when comparing groups who use peritumoral injections and the same radioisotope formulation (see Table 1). A good example is the rate of IMN drainage seen at two Australian institutions. Even though both groups use peritumoral injections of antimony sulfide colloid, the rate of IMN drainage reported at that time was 45% versus 6% [24, 31]. The only possible explanation for this is subtle differences in technique can account for large changes in demonstration of IMN drainage. In part, this will relate to the often small size of IMN and their tendency not to retain radioisotope as well as usually larger axillary nodes. This fickleness is compared with the robustness of lymphoscintigraphy for demonstrating axillary node drainage. This can be demonstrated easily when the radioisotope has been placed in all areas of the breast, including deep injection of radioisotope, sub- or intradermal injection, subareolar injection or even just blue dye mapping in experienced hands [20, 24, 25]. Under any of these circumstances, axillary sentinel nodes (SNs) can be demonstrated in >90% of cases. These findings have led many to conclude that IMN drainage is not real.

## contemporary anatomy

For many years, the anatomical concept of breast lymphatic drainage was that there is a rich network of lymphatics all draining into a subareolar plexus and then directed to the axilla in larger lymphatic collectors. In addition, a deep lymphatic plexus was described which also drained to the axilla [45]. In 1959, Turner-Warwick [46] convincingly demonstrated that the subareolar plexus was not a key part of the lymphatic drainage of the breast. He found that the lymphatic collectors



**Figure 1.** Complex lymphoscintigraphic mapping demonstrated with clear resolution of axillary and internal mammary nodes using technetium-labeled antimony sulfide colloid.

passed through the breast parenchyma or drained to more superficial collectors in the subcutaneous fat which then drained to the axilla. He also described collectors passing from the posterior surface of the breast to penetrate the pectoralis major muscle and deep fascia, which then passed through the intercostal spaces before coursing medially to reach the IMN [46]. Recent anatomical studies have further confirmed a model of breast lymphatic drainage that comprises superficial, deep and perforating systems [47]. These authors reported that the superficial system drains to the axilla, usually to a lymph node just behind the pectoralis minor muscle. The deep system drains to the axilla and also interacts with the perforating system which drains to the IMNs. In the publication by Suami et al. the authors found the perforating system does not interact with the superficial system [47]. Thus, the frequency of IMN drainage tends to reflect the method of lymphoscintigraphy, where peritumoral (deep lymphatic system) injections have a much higher frequency of IMN drainage than subareolar or subdermal (superficial lymphatic system) injections. This anatomical modeling corresponds precisely with the experience with high-quality lymphoscintigraphy and has been noted by us and other authors for many years now [29, 30]. These lymphatic anatomy concepts are demonstrated in Figure 2.

## contemporary lymphatic anatomy as indicated by lymphoscintigraphy

Even in centers where peritumoral injections are used, the widely varying rates of IMN drainage on lymphoscintigraphy are central to the argument about the relevance of IMN biopsy. In a practice where  $\leq 2\%$  of tumors have lymphatic drainage to the IMN, this discussion seems ridiculous. However, as can be seen in Table 1 several authors report drainage up to 38%–45% of their cases. This magnitude of difference seems inexplicable. Ideally anatomy should answer the question of how often different areas of the breast drain to the IMNs. For technical reasons, the elegant demonstrations of Suami et al. [47] discussed above do not allow this type of data to be obtained by their direct visualization method (G. B. Mann, personal communication).

## methods and results

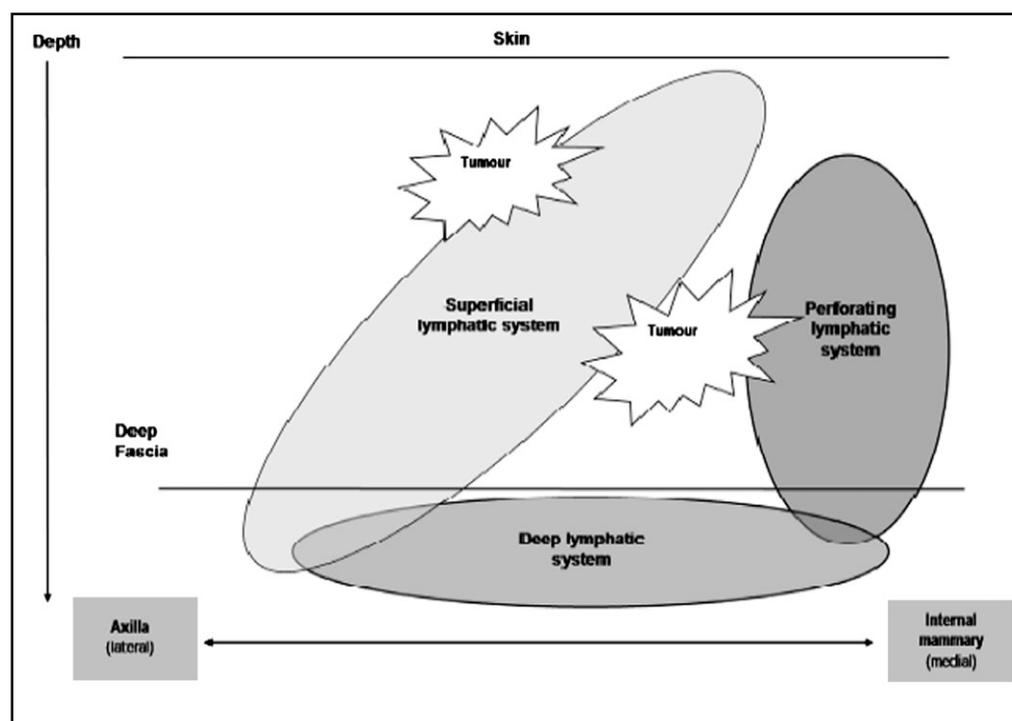
We reviewed two unrelated nuclear medicine departments' performance at demonstrating IMN lymphatic mapping over the periods of time they have carried out lymphoscintigraphy. Each facility's prospective database was reviewed to document their yearly IMN drainage rates on lymphoscintigraphy over 15 and 7 years, respectively. Lymphoscintigraphy was done at both using a technique of peritumoral injection with technetium-labeled antimony sulfide colloid. In facility U, all patients had ultrasound-guided injection of radioisotope. In facility C, all nonpalpable lesions had ultrasound guidance especially in the later part of the series. The two facilities identified axillary SNs in 95.5% and 93.6% of cases, respectively. Facility U had a mean of 34% IMN drainage rate. The yearly IMN drainage rate varied between 28% and 48% over the 15-year period (overall first 9 years 316 cases at a rate of 40% while later 6 years 1438 cases at a rate of 33%) (Figure 3). Facility C had an overall IMN drainage rate of 29%. The initial drainage rate of 19% fluctuated up to 36% over the 7-year period (overall first 4 years 186 cases at a rate of 25% while later 3 years 421 cases at a rate of 31%) (Figure 3). The overall lymphatic drainage

**Table 1.** Rates of lymphatic mapping to internal mammary nodes by lymphoscintigraphy technique

First author	Number of patients	Percentage IM drainage	Radioisotope; dose; injection site
Uren [24, 29]	159	45	Antimony sulfide; 10–28 MBq; 0.2–0.4 ml; pt
Kollias [31]	117	6	Antimony sulfide; 40 MBq; 0.5–4 ml; pt
Roumen [32]	66	14	Colloidal albumin; 60 MBq; 2 ml; pt
Roumen [33]	85	11	Colloidal albumin; 60 MBq; 2 ml; pt
Reuhl [34]	96	2	Colloidal albumin; 54 MBq; 0.5 ml; pt
Borgstein [35]	130	16	Colloidal albumin; 40 MBq; 4 ml; pt
Estourgie [36]	691	22	Nanocolloid albumin; 115 MBq; 0.2 ml; it
Jansen [37]	113	15	Colloidal albumin; 40–60 MBq; 0.2 ml; it
Van der Ent [38]	256	25	Nanocolloidal albumin; 370 MBq; 1 ml; pt
Moffat [39]	70	9	Sulfur; 37 MBq; 4–8 ml; pt
Hill [40]	35	7	Sulfur; 11 MBq; ni; pt
Johnson [41]	80	7	Sulfur; 37 MBq; 4–8 ml; pt
Noguchi [42]	41	12	Albumin; 111 MBq; 0.3 ml; pt
Imoto [43]	43	7	Tin or abumin; 30–50 MBq; 2.5 ml; pt
Shimazu [23]	40	38	Tin colloid; 30–80 MBq, subtumoral

Table modified significantly from Cserni and Szekeres [44].

IM, internal mammary; pt, peritumoral; it, intratumoral; ni, not indicated.



**Figure 2.** (Modified) Suami et al. model of breast lymphatic anatomy [47]. Tumor location in depth and medial versus lateral site relates to the observed lymphatic drainage pattern.

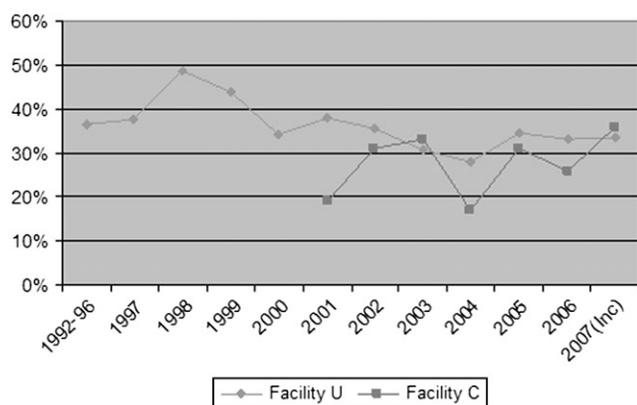
results at facility U in a consecutive series of 1754 patients' IM drainage occurred in 53% of medial tumors, 37% midline tumors and 24% of lateral tumors (overall 34%). These data are described in more detail and are documented in Table 2.

## discussion

### improving lymphatic mapping IMN rates

The increasing IMN drainage rate at facility C was associated with increasing volume of cases and modifications in technique

including increased use of ultrasound to localize the tumor. The practice also had upgrades of collimators and increasing awareness of the referring surgeons' interest in this pathway of lymphatic drainage. These data indicate that the rate of IMN drainage is around one-third of the axillary drainage rate. Technical modifications have resulted in facility C converging on this parameter which has been maintained over many years by facility U. It is our opinion that in the absence of a reliable anatomical model, high-quality lymphatic mapping with peritumoral injections is the best known demonstrator of breast



**Figure 3.** Facility U—15-year experience of internal mammary node drainage and facility C—7-year experience of internal mammary node drainage on lymphoscintigraphy.

**Table 2.** Facility U lymphoscintigraphy rates for 1754 consecutive cases

	Medial tumors, n = 406	Central and midline tumors, n = 394	Lateral tumors, n = 943	All tumors, n = 1754
AN	90.2	96.2	97.6	95.5
Not AN	9.9	3.8	2.4	4.5
IMN	52.7	37.8	24.4	33.9
Not IMN	47.3	62.2	75.6	66.1
Neither IMN nor AN <sup>a</sup>	3.9	2.8	2.1	2.7
IMN, not AN <sup>a</sup>	5.9	1.0	0.3	1.8
Total <sup>b</sup>	23.2	22.5	53.6	100.0

AN, axillary node lymphatic drainage; IMN, internal mammary node lymphatic drainage.

lymphatic anatomy. An institution finding lower rates of IMN drainage reflects technical issues and not the anatomy of the breast. The remarkably constant rate of positive lymph nodes irrespective of the IMN drainage rate (discussed below) is supportive of these conclusions. Further supportive evidence is the rate of positive IMNs in the review of ERM series by Bevilacqua et al. [27] is 18.8% in unselected series compared with the axillary node positivity rate of 48%. This ratio approximates 39% which is similar to the high-quality lymphoscintigraphy rates of IMN drainage. Also in Bevilacqua's review, the rate of IMN positivity in nonselective case series in the axillary node-positive cases was 31% [27]. This implies that SNs in both node fields were at some stage positive and thus the ratio of axillary to IMN positivity should be a reflection of the anatomical density of the lymphatics draining to each. Again, these data are in a consistent range similar to the lymphatic drainage rate from high-quality lymphoscintigraphy.

**relevance of IMN biopsy**

Transpectoral IM biopsy of SNs mapped on lymphoscintigraphy is of debatable relevance. This is principally due to the lack of conviction that it is a valuable addition to the staging information derived from standard

histopathology and axillary assessment [26]. It is also due in part to the technical difficulty of surgical access, concern about potential complications of the procedure and a lack of technical expertise among many breast surgeons. Furthermore, many authors question the validity of IM biopsy in this day of early breast cancer diagnosis where most decisions on systemic therapy are made on primary tumor characteristics and increasingly on tumor genetic profiling. One publication recommended that by using a selection algorithm, IM biopsy should be reserved for tumors that are subcentimeter, medial location and proven to be axillary node negative. The authors argued that adjuvant treatments will not be changed otherwise [27].

Others have argued from clinical experience that the information from IMN biopsy changes management in a significant minority of patients [48, 49]. Higher level evidence of the contemporary relevance of IMN positivity can be extrapolated from two at first seemingly unrelated data sources. First, review of large databases has shown that medial tumors have a worse prognosis than lateral tumors [50–53]. This has been explained in all situations by the higher rates of IMN involvement being underrecognized (under staging) and therefore patients being effectively undertreated with adjuvant therapy. The second line of evidence is from a series of 604 early breast cancer patients including 104 who had IMN drainage but none of the IMNs were biopsied. The 5-year overall survival and recurrence-free survival outcomes were worse in those patients with IMN drainage. Axillary node-positive patients with lymphatic mapping to IMN had a 3.3-fold higher mortality risk (trending toward significance) [54]. This possibly indicates that even without the knowledge of the results of transpectoral IMN biopsy, the presence of anatomically identifiable IMN drainage may be enough prognostic evidence to influence management. For instance, from the ERM era, in circumstances where the patient is young, the tumor is large and medial, and the axilla is known to be positive then there maybe in excess of 40% chance of a positive result [3]. If you further select this case type by the demonstration of IMN lymphatic drainage, it is debatable whether transpectoral IMN biopsy is indicated as a strong case can be made for IMN radiotherapy in any case. These separate sources of data indicate relevance to doing lymphoscintigraphy with or without transpectoral SNB in all women including those with known positive axillary nodes.

**IMN positivity rates**

Even though the rates of IMN drainage vary widely on lymphoscintigraphy, there is evidence from a number of sources that there is a similar and significant frequency of positive IM sentinel lymph node metastasis. This rate ranges in a narrow band from 13% to 23.5% of the cases that have IMN drainage on lymphoscintigraphy who are able to be successfully biopsied (Table 3). This is in groups of patients who were clinically axillary node negative in the vast majority of cases and hence SNB was being done principally to stage the axilla. The ERM series mentioned above document several noteworthy points. First, the rate of IMN metastasis is significantly higher when the axilla is positive. Secondly, the rate of IMN metastases

**Table 3.** Rates of internal mammary drainage and positivity compared with axillary status in contemporary series

Author, total number of SNB cases	Year, country	% Ax positive	% IMN drainage	% IMN biopsied	% IMN positive	% IMN + if ALN negative
Madsen [48], <i>n</i> = 506	2007, The Netherlands	41	22	78	24	N/A
Farrús [55], <i>n</i> = 225	2004, Spain	27	14	69	14	0
Hong [49], <i>n</i> = 979	2005, Australia	32	15 (33 <sup>a</sup> )	88	18	4
Paredes [56], <i>n</i> = 383	2005, Spain	N/A	14	73	25	20
Leidenius [57], <i>n</i> = 984	2006, Finland	40	14	88	15	44
Estourgie [36], <i>n</i> = 691	2003, The Netherlands	33	22	87	17	7
Dupont [58], <i>n</i> = 1273	2001, USA	N/A	2.4	N/A	14	6
Mansel [59], <i>n</i> = 707	2004, UK	26	10	45	13	6
Spillane [60], <i>n</i> = 100	2008, Australia	33	31	81	20	60

<sup>a</sup>Initial figure is surgeon reported; figure in parentheses is obtained after publication directly from nuclear medicine facility. Ax, axillary lymph node positive rate; ALN, axillary lymph node; N/A, not available.

is nearly double when assessing medial/central tumors versus lateral tumors. Clearly, the likelihood of metastases to these IMNs relates to the frequency of lymphatic drainage to IMN from these different regions of the breast. Thirdly, the overall rate of IMN positivity in the review of ERM series, when adjusted for selection bias, was 18.8% [27]. This is about three to four times the current SNB series range which ranges from ≤4% to 7% of all cases (20% of the ~34% of cases that have IMN mapping) (Table 3). The ERM series have ~50% of cases with positive axillary nodes often with clinically apparent disease, compared with more recent studies where most SNB series have axillary node positivity rates ranging from 26% to 41% but in patients who are clinically axillary node negative [24, 33, 59]. This significant stage migration in axillary node positivity and disease burden rates with earlier diagnosis would intuitively be expected to reflect in a similar quantum stage migration with the rate of IMN positivity. Even taking this into account, the current reported rates of IMN-positive nodes in units doing transpectoral SNB indicate that the rate of IMN positivity is still lower than you would expect from this extrapolation. This raises the question of a significant false-negative result from transpectoral IMN biopsy. Other confounding factors in interpretation of these data include the possibility of a selection bias in the current SNB series for medial cases where the information from the IMN SNB is thought to be more relevant and a separate surgical incision would not be necessary. This is not obvious from the publications but is possible. However, if this was happening, it would indicate a higher false-negative rate in the biopsy technique as the IMN-positive rates should be higher in medial sector tumors. On the other hand, another factor that may lead to underestimation of positivity rates in the old ERM series is the different pathology protocols used for assessing SNBs compared with lymph node assessment before SNB. This may have led to missed IMN micrometastatic disease in the ERM series. Although the rates of micrometastatic disease were not discussed in the ERM series, the ratios of IMN to axillary node positivity should remain an accurate reflection of breast lymphatic pathways and this should still be relevant today. In the ERM study by Veronesi et al. [3], the rates of IMN positivity ranged up to 44% in axillary node-positive women who were <40 years old and had medial tumors >2 cm in

maximum diameter. Even in axillary node-negative younger women, it was up to 17% IMN positivity. This study, as did the others related to adjuvant therapy naive ERM, demonstrated very significant prognostic importance of this information equivalent to that derived from axillary node status if either was positive but doubly worse if both were positive [3, 5]. Again, it should be emphasized that this is not just information that confirms ‘node positivity’.

### survival impact of IMN metastasis

There is strong evidence that patients with IM metastasis have significant reduction in survival. Historical series of ERM demonstrated poor survival of these patients at all stages [3, 12, 61]. The ERM series are essentially observational in that the diagnosis of IMN disease did not change adjuvant systemic therapy. For the most part, chemotherapy and radiotherapy was not given. Certainly, the results of the IMNs did not lead to changes in management that have subsequently been shown to be effective in improving survival. Thus, in the randomized controlled trial of the International Cooperative Group, the survival equivalence was a test of surgery’s ability to improve survival, not a test of the information derived from IMN biopsy to alter the systemic and radiotherapy managements that are now known to improve survival [11, 12]. As will be discussed in the subsequent paragraph, a recent publication by Veronesi et al. [62] suggest an influence on survival from taking the results of IMN biopsy and giving IMN/supraclavicular radiotherapy for positive cases.

### IMN sampling

Veronesi et al. have recently published their results of sampling from the upper intercostal spaces in medial breast cancers. In this series, 38% of cases were guided by the gamma probe after peritumoral injection of radioisotope. The positivity rate was 11% in these cases and 9.8% in the remaining women whose IMN biopsies were not guided by a gamma probe. Overall 68 of 663 patients had positive IMN. The patients with positive nodes all had IMN radiotherapy. The cohort’s excellent 5-year survival was in part attributed to this radiotherapy [62].

Exploring the second and third intercostal spaces would identify just over half of our IMN SN sites.

### false-negative rates of IMN biopsy

IMN biopsy is a technically challenging procedure in some instances. This is particularly in the lower intercostal spaces where the gap between the ribs is smaller. When identified on lymphoscintigraphy, the rates of successful IMN SN retrieval reported in the literature range from 45% to 88% [36, 49, 59]. This is from centers interested in the procedure. The difficulties not often discussed include if a lymphoscintigraphy indicates hot spots in multiple intercostal space levels, are they all SNs or are some second tier lymph nodes? It is known that IMNs are less efficient at retaining radiocolloids than are axillary nodes. A single collector may thus radiolabel a string of IMNs but only the lowest node directly receiving the draining collector is the true SLN. Thus, how many spaces need to be explored? Removing a lymph node from the indicated space does not necessarily mean it was the SN as there are often multiple lymph nodes at each level. The use of peritumoral injections for lymphoscintigraphy in medial tumors may have a shine through effect making lymphatic mapping less reliable. The hot and/or blue node may also be under the rib and not retrievable in some cases. Lateral tumors with IMN drainage may not be explored because of the concern about having to make a cosmetically unpleasant separate incision. These factors all add to the potential for a false-negative transpectoral IMN biopsy.

### IMN biopsy and minimal access breast surgery

A number of authors have now documented that the majority of IMN SNB can be done through the breast incision and there is no need for a separate parasternal incision in the majority of cases [63]. In a series of 100 cases of attempted minimal access breast surgery for axillary and IMN SNB, only 1 of 21 IMN SNBs required a separate incision. That patient had augmentation implants [60].

### management altering potential of IMN biopsy results

If the IMN is positive after transpectoral biopsy, there is a strong indication from the literature that most radiation oncologists will recommend radiotherapy to that area [48, 49, 62]. Conversely, if the IMN is not positive, many radiation oncologists use that information to guide them against giving radiotherapy to that area. If it is a high-risk case for loco-regional relapse, then the absence of IMN drainage on lymphatic mapping may be used by some centers as a guide to indicate no probability of additional benefit to IMN radiotherapy. Depending on the axillary node status, the decision to give postmastectomy radiotherapy or not may be determined by any additional IMN involvement. Until results from current clinical trials are available many centers use three or more axillary nodes as their threshold for postmastectomy radiotherapy.

In light of our concerns regarding the false-negative rate of both IMN sampling and IMN SNB, there may be a reasonable argument to give radiotherapy to high-risk patients who demonstrate IMN mapping on good quality lymphoscintigraphy. However, more research would be

needed if IMN mapping were used as a surrogate marker to guide adjuvant radiotherapy decisions. There is growing evidence that good quality chest wall radiotherapy alone confers a survival benefit and this maybe in part due to inadvertent treatment of these nodes [64]. The exact role of IMN radiotherapy in any situation is still controversial as was fully discussed in Bevilacqua's review [27]. This is unlikely to be resolved by the European Organization for Research and Treatment of Cancer Trial (EORTC-22922) as cases were not selected using information from high-quality lymphoscintigraphy.

As also pointed out by Bevilacqua et al. [27], the decision on whether to give chemotherapy or not is not often solely based on having a positive IMN. This is because many such decisions are made on primary tumor characteristics. Another reason cited is that most cases of IMN positivity also have axillary lymph node positivity [27]. However, a positive IMN result may contribute information that alters the amount of chemotherapy given, particularly if working in a center that escalates the number of cycles of chemotherapy based on the degree of lymph node positivity. An underrecognized factor, when making adjuvant therapy decisions in this situation, is that axillary and IMN positivity has been associated with a doubly worse prognosis in the past. In the small tumors with negative axillary SNB but positive IMN SNB, this information maybe crucial to determining whether to have chemotherapy.

### conclusions

IMN drainage on lymphoscintigraphy is more difficult to demonstrate than axillary node drainage. This is due to technical reasons and not the absence of anatomically real lymphatics to the IMN. There are multiple sources of data indicating that IMN drainage occurs in about one-third of breast cancers but is more common in medial tumors. There is evidence now that therapy is altered in a substantial proportion of patients by the knowledge of IMN drainage and biopsy of IMN by transpectoral SNB. There is evidence that survival is worse in patients who have IMN drainage ignored when planning adjuvant therapy. The best way to clarify the situation is to design a clinical trial designed for assessing these areas of controversy. This would be the only way to resolve the importance of IMN in a contemporary population of breast cancer patients.

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## **CHAPTER 3:**

**High discordance rates between sub-areolar and peritumoural breast lymphoscintigraphy.**



## High discordance rates between sub-areolar and peri-tumoural breast lymphoscintigraphy

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### Abstract

**Objective:** To test the hypothesis that sub-areolar (SA) lymphoscintigraphy (LSG) identifies the same sentinel node as peri-tumoural (PT) injections.

**Background:** It is commonly believed that all LSG techniques will identify the same sentinel lymph nodes (SLN) draining the breast. Hybrid imaging technology (SPECT/CT) allows accurate identification of the exact location of SLNs. Using SPECT/CT SA and PT LSG techniques were compared.

**Method:** In a multi-centre trial 39 patients sequentially underwent LSG (SA followed by PT) separated by 2–7 days. Patients were referred by 4 surgeons to 3 LSG centres, with standardization of isotope (99mTc-antimony sulfide colloid), LSG and SPECT/CT evaluation techniques. LSG were evaluated for SLN concordance and degree of discordance in the axilla and internal mammary nodes (IMN).

**Results:** 39 eligible patients, median age 62 years, were recruited. Successful axillary SLN mapping for SA and PT injection techniques was 87% and 95% respectively. Successful internal mammary SLN mapping occurred with SA and PT LSG in 5% and 36% respectively. Discordance was identified in the IMN (39%) and axilla (21%), with an overall rate of discordance between SA and PT LSG of 56%.

**Conclusions:** There is a high level of discordance in the localization of SLN by these commonly used LSG injection techniques. This discordance has implications for accuracy of axillary and extra-axillary staging and could impact on patient outcome.

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**Keywords:** Sentinel lymph node; SPECT/CT lymphoscintigraphy; Breast cancer; Axilla; Internal mammary

### Introduction

Despite advancements in molecular staging of breast cancers, sentinel lymph node (SLN) evaluation remains

important for oncologists planning adjuvant loco-regional and systemic therapy.

Several different lymphoscintigraphy (LSG) injection techniques are now in use, with claims that they all identify the same axillary sentinel nodes.<sup>1–3</sup> Proponents quote historical studies claiming the breast to be a single ectodermal unit draining to the anteropectoral axillary lymph nodes. Recently both anatomical and clinical studies have clearly

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demonstrated the contention that all methods of LSG map to the same anterior pectoral axillary SLN to be incorrect.<sup>4–7</sup>

With the advent of hybrid imaging with SPECT/CT technology the anatomical location of SLN has been greatly enhanced.<sup>4,8</sup> Exact locations of lymph nodes can be determined with relation to surrounding anatomical landmarks. Direct comparisons of different LSG techniques can now be performed with a high level of accuracy rather than the reliance on adjuncts such as intra-operative blue-dye injections.

It has previously been shown that if the same LSG technique is used on separate occasions the same SLN are demonstrated on LSG in breast cancer patients.<sup>9</sup> To our knowledge there has not been a study that directly compares the exact anatomical location of SLNs with different LSG injection techniques in the same patient using SPECT/CT technology. The aim of this study was to test the hypothesis that sub-areolar (SA) LSG identifies the same SLN as peri-tumoural (PT) injections, both in the axilla and non-axillary lymph node basins. Discordance in the axilla has not been previously demonstrated.

## Method

In a multi-centre trial, four surgeons recruited patients who underwent double sequential LSG (SA followed by PT) at three separate nuclear medicine facilities (Nuclear Medicine and Diagnostic Ultrasound at Royal Prince Alfred Medical Centre, North Shore Nuclear Medicine at Mater Hospital and Dee Why Nuclear Medicine). Surgery was performed at four different institutions (Mater, Manly, Royal North Shore and Strathfield Private Hospitals).

The LSGs were separated by 2–7 days to allow washout of radiocolloid. Injection and LSG techniques were standardized across the 3 nuclear medicine facilities. Inclusion criteria included women with biopsy proven early breast cancer with a clinically negative axilla requiring SLN evaluation. Patients with locally advanced breast cancer, those undergoing neo-adjuvant therapy and male patients were excluded from the trial.

## Data collection

From February 2009 to July 2011 data was collected from women undergoing dual LSGs. The clinical demographic data gathered included age, body-mass index, breast density, breast size, menopausal status and previous breast history. Surgical data collected included details on surgery, site, number of SLNs harvested, subsequent axillary dissection and intra-operative correlation to LSG findings. LSG data collected included location and depth of tracer injection, number and location of axillary and extra-axillary SLN. The pathology on all patients were analysed separately at each centre and results collated.

## Lymphoscintigraphy technique

Standardized techniques of SA and PT LSG has been previously described.<sup>4</sup> The location of the breast cancer was assigned to one of nine segments. This placed the cancer as lying either in one of the four standard breast quadrants (upper outer, upper inner, lower outer and lower inner), behind the nipple or at the junction of two quadrants to give nine breast segments in each breast (Table 2).

For the PT study, four peri-tumoural injections of radiocolloid, <sup>99m</sup>Tc-antimony sulfide colloid, were performed with ultrasound guidance in all non-palpable and some palpable tumours. Four injections of the radiocolloid (10–40 MBq depending on timing of surgery) were placed around the margins of the tumour at the mid-pole of its depth at 12, 3, 6 and 9 o'clock. For SA LSG, two injections of <sup>99m</sup>Tc-antimony sulphide colloid (20–40 MBq) were given in the sub-areolar space in the upper outer quadrant of the breast. For both injection techniques following injection of the tracer, massage in a rotary motion was performed by the patient for five minutes and then an early high resolution planar digital image were acquired in the supine anterior, left anterior oblique, lateral and sitting projections, each for five minutes to identify the lymphatic collectors reaching the SLN or nodes. Delayed planar images were performed at one to three hours depending on the rapidity of tracer movement through the lymphatics. SPECT/CT imaging was also performed at this time and the surface location of the SLNs marked on the skin with an indelible pen. The exact anatomical location of each SLN in the axilla, internal mammary chain and elsewhere was reported.

## Discordance/concordance analysis

Discordance was defined by direct comparison of the SPECT/CT imaging of both studies. Discordance was defined as:

- Type 1: One study identified SLN(s) in the axilla or IMN and the other study demonstrates none
- Type 2: Both studies identified SLN(s) in the axilla or IMN however they were all different nodes
- Type 3: Both studies identified SLN(s) in the axilla or IMN however only some nodes were different

Concordance was defined as:

- Type A: Identical SLN(s) in the axilla or IMN.
- Type B: No drainage to any SLN(s) in the axilla or IMN.

## Statistical analysis

Analyses comprised of descriptive statistics and concordance comparisons of proportions. Statistics relating to concordance comparisons were performed using the

conditional binomial exact test<sup>10</sup> and the potential effects of variables on discordance were explored using logistic regression. Variables analysed were age, BMI, breast size, density, menopausal state, tumour position, PT injection distance from nipple and depth of PT injection. Confidence intervals for the proportions were calculated using the modified Wilson method.<sup>11</sup>

#### Ethics and radiation safety

Ethics approval was granted by NSW Health, protocol number X08-0327. The protocol of the study was presented to the Royal Prince Alfred Hospital Radiation Safety Committee who determined a low cumulative radiation exposure ( $\sim 2\text{mSv}$ ) with the use of low dose CT scan. At this level it was determined not to be harmful to participants.

#### Results

Forty-four patients were recruited to this study, however five patients withdrew consent. Thirty-nine evaluable patients underwent double sequential LSG (SA followed by PT) separated by two to seven days. PT LSG is the locally established standard technique, and all participants underwent this prior to breast surgery.

#### Demographics

Patient demographics, LSG, surgical treatment and pathology data are summarized in Tables 1–3, Fig. 1. The rate of successful axillary SLN mapping in SA and PT injection techniques were 87% and 95% respectively. The rate of successful internal mammary SLN mapping in SA and PT were 5% and 36% respectively. Two patients failed axillary lymphatic mapping using PT LSG and SA LSG. One of these two patients did not demonstrate any IMN drainage either and underwent an axillary clearance that demonstrated metastasis. The second patient had IMN drainage on PT LSG only and underwent axillary sampling which did not identify any metastasis. Aside from two other patients with additional intra-mammary SLNs there was no other atypical lymphatic drainage.

#### Concordance and discordance

Discordance and concordance analysis between the two studies is listed in Tables 4 and 5 respectively. The overall rate of discordance was 56%. Of note the concordant IMN LSGs were only so because neither study demonstrated any IMN SLN. There were no studies that identified identical IMN in both SA and PT LSG. In addition all three patients with type 1 axillary discordances were identified by PT LSG only. Twelve out of thirteen patients with type 1 IMN discordances were identified by PT LSG only and only one by SA LSG.

Table 1  
Patient characteristics and surgery details.

		N	%
		(N = 39)	
Age (years)	Median	62	
	Range	35–76	
Breast size	Large (>600 g)	14	36
	Small–mod (<600 g)	25	64
Breast density	High density (>50%)	14	36
	Low density (<50%)	23	59
	Not available	2	5
Menopausal status	Pre-menopausal	12	31
	Peri-menopausal	2	5
	Post-menopausal	25	64
Initial surgery	Breast conserving	33	85
	Mastectomy	6	15
	Axillary clearance	9 <sup>b</sup>	23
Axillary SLNB (n = 37)	Successful	37	100
	Metastasis	10	<sup>a</sup>
IM SLNB (n = 14)	Successful	9	64
	Metastasis	0	0

SLNB = sentinel lymph node biopsy.

IM = internal mammary node.

<sup>a</sup> Final number of patients with axillary metastasis were 11 of 39 (28%) including one patient with axillary dissection for failed LSG.

<sup>b</sup> One axillary clearance performed for large primary with no metastasis; Two patients did not undergo axillary dissection (one with micro-metastasis).

#### Factors predicting discordance

The conditional binomial exact test analysis to determine factors predicting discordance in the two techniques found tumour position as the only significant factor. Patients with medial and central tumours compared to lateral tumours were five times more likely to be discordant between the 2 techniques compared to lateral tumours ( $p = 0.2$ ; Odds ratio = 5.2; 95% CI: 1.3–20). This significance reflects the greater percentage of patients with lymphatic drainage to the IM SLNs from medial and central tumours in PT LSG.

#### Discussion

The principle of SLN biopsy is to remove the true SLNs receiving direct lymphatic drainage from the primary tumour site with the assistance of LSG thereby reducing patient morbidity. This anatomical study was a proof of principle that one cannot assume that injection of radio-colloid in any area of the breast will demonstrate the same lymphatic channels and SLN as it would with a peritumoural injection of tracer. Although this study was adequately powered to demonstrate a difference between PT and SA LSG, further analysis of factors determining discordance, pathological and clinical outcomes cannot be assessed due to the sample size and lack of randomization. However it would be intuitive to conclude that peritumoural LSG would be more accurate based on long held tenets of the LSG technique. i.e. injecting closer to the tumour is more accurate than injecting into a region.

Table 2  
Tumour characteristics.

		N	%
		(N = 39)	
Tumour size (mm)	Average (Mean)	23	
	Range	3–76	
Tumour location	Upper inner quadrant	4	10
	Junction of upper and lower inner quadrants	1	3
	Lower inner quadrant	2	5
	Junction of upper inner and outer quadrants	9	23
	Junction of lower inner outer quadrants	4	10
	Upper outer quadrant	11	28
	Junction of upper and lower outer quadrants	3	8
	Lower outer quadrant	5	13
	Nipple area	0	0
	Pathology	Infiltrating duct cancer	29
Infiltrating lobular cancer		7	18
Tubular cancer		1	3
DCIS/benign		2	5
Grade	1	9	24
	2	14	38
	3	14	38
Hormonal status	ER+	32	86
	PR+	27	73
	HER2+	3	8
Lymph node status	Overall axillary metastasis	11 <sup>a</sup>	28
	Axillary metastasis in Axillary disconcordant LSG (n = 8)	3	
	Axillary metastasis in Axillary concordant LSG irrespective of IMN drainage (n = 31)	8	
	IMN metastasis	0	0

DCIS = ductal carcinoma insitu.

ER+ = oestrogen receptor positive.

PR+ = progestogen receptor positive.

HER2+ = Human Epidermal Growth Factor Receptor 2 positive.

<sup>a</sup> 1 pt with micro-metastasis.

### Lymphoscintigraphy techniques and lymphatic mapping

Several different LSG injection techniques are now in use, with proponents claiming identical axillary

Table 3  
Lymphoscintigraphy results.

	Sub-areolar (N = 39)	Peri-tumoural (N = 39)
Successful axillary SLN mapping	34	37
Percentage successful	87	95
Mean axillary SLNs	1.3	1.4
Range	0–3	0–4
Successful IMN SLN mapping	2	14
Percentage successful	5	36
Mean IM SLNs	0.1	0.6
Range	0–2	0–3

SLN = Sentinel lymph node.

IMN = Internal mammary node.

drainage.<sup>1–3</sup> They support this contention based on historical studies claiming the breast to be a single ectodermal unit draining to the anteropectoral axillary lymph nodes. Initial descriptions of lymphatic mapping involved peritumoural injections.<sup>12</sup> However, in the USA various institutions initial attempts at mammary LS using PT injections of the large particle radiocolloid <sup>99m</sup>Tc sulphur colloid often failed as very little of the tracer left the injection site. Injecting the tracer away from the tumour site was found to be more successful in radiolabelling a node in the axilla, particularly with intra-dermal and sub-areolar injections. This has become more commonly used around the world in part because of the increased speed of LSG. In some settings the predictable drainage to the axilla has been used as a reason not to perform a LSG at all, with intra-operative injection of radiocolloid and subsequent biopsy performed with the assistance of a gamma probe.<sup>13</sup>

However recent anatomical and clinical studies have challenged the contention that all methods of LSG techniques map to the same SLN.<sup>4–7</sup> With the introduction of hybrid SPECT/CT imaging techniques it is now possible to accurately identify the anatomical site of the SLN which vary significantly.<sup>4</sup> This study provides direct evidence to support this contention. In addition the cost and irradiation from hybrid SPECT combined with low dose CT imaging techniques is minimal compared to the overall gain in staging accuracy.<sup>4</sup>

### Lymphoscintigraphy discordance

This study also highlights several important factors when considering the appropriate technique for breast LSG. First, it demonstrates a significant discordance in axillary lymphatic mapping of 21% (8 of 39 patients) between the two techniques (Table 4, Fig. 1). Second, it highlights significant discordance in mapping of the IMN at 38.5% (15 of 39 patients; Table 4). Clearly sub-areolar techniques of LSG fail to stage the IMN. Finally techniques in achieving high rates of IMN mapping have been described by the authors<sup>4,5,14</sup> and these have been successfully applied in the three separate nuclear medicine facilities involved in the study.

Although axillary discordance of 21% is quite significant, this can only result in a false negative axillary staging rate of approximately 7–8%, given 1/3 of patients have axillary metastasis. This false negative rate would be even lower if one were to account for improvements in axillary staging with concurrent blue-dye injection, partial LSG concordance, intra-operative examination of the axilla and the common practice of removing additional non-sentinel lymph nodes.<sup>19</sup> Finally the increasing practice of breast conserving surgery results in the unintentional treatment of the lower axilla with adjuvant breast radiotherapy,<sup>15</sup> which would result in fewer clinical recurrences. Similarly missed IM sentinel node metastasis would rarely present as

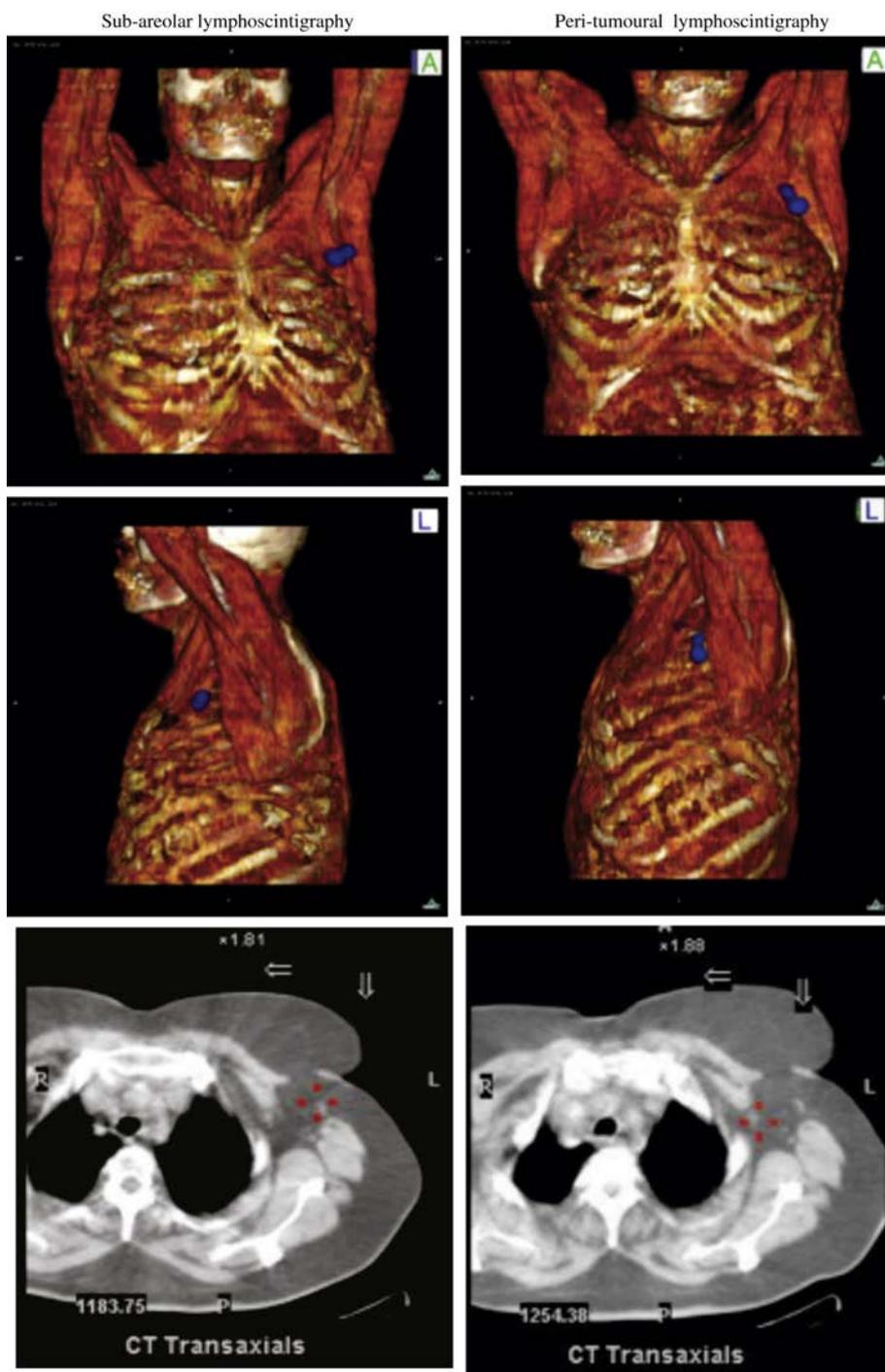


Figure 1. Discordant Axillary Lymphoscintigraphy.

a clinically apparent recurrence. Rather it is plausible untreated IMN metastasis may result in pleural, pulmonary and distant disease rather than chest wall recurrences due to the impact of tangential radiotherapy fields after breast

conserving surgery. Despite the significant discordance evident in LSG techniques, all of the above factors may account for the success of SA LSG without impacting clinical outcome.

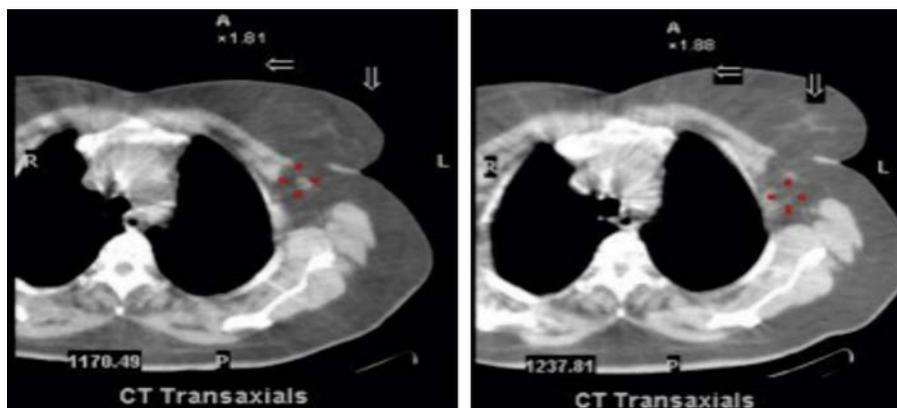


Figure 1. (continued)

*Management of axillary sentinel lymph node metastasis*

With the evidence from several recent randomized controlled trials there is now confusion as to the appropriate management of metastatic disease to the axillary SLNs. While surgeons are doing fewer axillary clearances with the results of the ACOSOG Z11 and circumstances surrounding the early closure of IBCSG 23.01<sup>16,17,33</sup> the radiation oncologists are being encouraged to irradiate more regional nodes as indicated by the results of the MA.20 intergroup trial (T. J. Whelan et al. ASCO 2011 Abstract LBA1003) and EBCTCG meta-analysis.<sup>18</sup> In such an environment the importance of accurate LSG would be amplified. Surgeons missing or not treating low volume axillary disease could result in these patients being under-staged, possibly not receiving adjuvant systemic therapy and more likely missing appropriate loco-regional radiotherapy.

Table 4  
Discordance evaluation.

	Sub-group	N	Subtotal	%	95% CI
		(N = 39)			
Axilla discordance only	Type 1	3	7	18	9.0–32.7
	Type 2	3			
	Type 3	1			
IMN discordance only	Type 1	13	14	36	22.7–51.6
	Type 2	0			
	Type 3	1			
Axilla and IMN discordance	Type 1 – Axilla	1	1	3	0.5–13.2
	Type 1 – IMN	1			
Either axilla or IMN discordance		22		56	41–47

IMN = internal mammary node; SLN = sentinel lymph node.  
 Type 1 = one study identified SLN and the other study no SLN.  
 Type 2 = both studies identified SLNs but all were different.  
 Type 3 = both studies identified SLNs but some were different.

*Internal mammary staging*

High rates of IMN drainage have been previously described and now replicated at two other facilities.<sup>4,5</sup> In this study the IMN drainage from PT LSG was evident in 36%; with an IMN to axillary lymphatic mapping ratio of 38%, which has also been previously predicted by modelling.<sup>14</sup> Furthermore this comparative ratio of IMN to axillary lymphatic mapping does reflect historical ratios of IMN to axillary metastasis of ~37% demonstrated in large clinical trials of extended radical mastectomy suggesting it is the appropriate rate.<sup>14,21</sup> The optimal staging and treatment of IMN SLN has been the centre of great debate. One cannot ignore the significant historical evidence of diminished survival associated with IMN metastasis.<sup>22,23</sup> In addition several recent epidemiological studies have demonstrated diminished survival for tumours located in the medial quadrants of the breast.<sup>24–28</sup> This would intuitively be a result of poor regional therapy to IMN metastases which are more prevalent in medially located breast cancers. Yet routine use of IMN radiation cannot be supported as it can lead to

Table 5  
Concordance evaluation.

	Sub-group	N	Subtotal	%	95% CI
		(N = 39)			
Axilla concordance only	Type A	29	31	79	9.0–32.7
	Type B	2			
IMN concordance only	Type A	0	24	62	22.7–51.6
	Type B	24			
Axilla and IMN concordance	Type A – Axilla	16	17	44	0.5–13.2
	Type B – Axilla	1			
	Type A – IMN	0			
	Type B – IMN	17			

IMN = internal mammary node; SLN = sentinel lymph node.  
 Type A = identical SLNs in axilla or IMN.  
 Type B = no drainage to any SLN in axilla or IMN.

significant cardio-respiratory morbidity and mortality.<sup>29</sup> However one may tailor regional radiotherapy for patients with known axillary metastasis and IMN lymphatic drainage on LSG. These patients may benefit from adjuvant IMN radiation.<sup>30,31</sup>

IM SLN biopsy can be a technical challenge for most breast surgeons. Even with experts it may not reach the desired accuracy of axillary SLN biopsy. As demonstrated in this study four different surgeons had an overall success of 64% (Table 1). However if LSG demonstrated IMN drainage and the surgeon did not attempt or failed to retrieve the SLN, then the patient could be a candidate for adjuvant IMN radiation if poor prognostic factors are present (young patient, proven axillary metastasis or other unfavourable tumour characteristics).<sup>14,30–32</sup> Hence accurate IMN LSG with the described techniques can result in accurate staging and radiation planning.

## Conclusion

This study has demonstrated discordance in axillary and IMN lymphatic mapping between SA and PT LSG. This refutes the conviction that the entire breast drains as a single ectodermal unit to the same sentinel nodes. Accurate LSG will enhance lymph node staging, which in turn assists with planning adjuvant therapy, particularly radiotherapy. In an environment of improving outcomes by small percentage increments for breast cancer patients, the impact of inaccurate axillary or IMN staging may become relatively more significant.

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## Conflict of interest statement

None declared.

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## **CHAPTER 4:**

**Internal mammary node metastasis in breast cancer:  
Predictive models to determine status & management  
algorithms.**

# Internal mammary node metastasis in breast cancer: Predictive models to determine status & management algorithms<sup>☆</sup>

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## Abstract

**Aim:** Internal mammary node (IMN) metastases are an important prognostic factor in breast cancer. However due to difficulty of access, most surgeons ignore these nodes, hence adjuvant treatment decisions may be compromised. Through mathematical modeling based on large datasets this study aims to estimate the current rate of IMN and sentinel node metastasis.

**Methods:** Models were created to estimate the current rate of axillary and IM sentinel node metastasis. Data from historical extended radical mastectomy series were analyzed to project contemporary rates of IMN metastasis. This information was coupled with derived models and contemporary datasets: a single-institution breast lymphoscintigraphy database (1992–2007) to establish lymphatic anatomy; and the Surveillance, Epidemiology and End-Results (SEER) registries in the US (2000–2003).

**Results:** Rates of IMN metastasis and positive sentinel nodes were estimated and models derived to assist with predicting IMN status in patients. If high definition peritumoral lymphatic mapping were available, the predicted rates of positive sentinel nodes in the axilla (AN) and internal mammary chain (IMN) would be equal. We predicted the overall rate of IMN metastasis is ~39% the rate of positive sentinel AN.

**Conclusion:** Simplified models and algorithms can predict IMN status.

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**Keywords:** Breast cancer; Internal mammary lymph node metastasis; lymphoscintigraphy; Modeling; Sentinel nodes; False negative rate; Staging

## Introduction

Internal mammary lymph node (IMN) metastasis in breast cancer is a well-documented prognostic factor, of similar importance to axillary-lymph-node (AN) status. Although randomized controlled trials in the 1970s failed to show a survival benefit of the dissection of these nodes during extended radical mastectomy (ERM), a procedure that included IMN dissection, they did demonstrate diminished survival of patients with IMN metastasis.<sup>1,2</sup> Survival usually halved in cases with both IMN and AN positivity. More recent epidemiological series have shown worse survival of patients with medial

than patients with lateral tumors.<sup>3–7</sup> All these studies concluded that a greater percentage of undiagnosed IMN metastasis and as a result under staging of these patients was responsible for the poorer survival and not inherently different tumor biology of medial tumors.

Since the demise of ERMs these nodes have been ignored until recently. The advent of sentinel node lymphatic mapping has rekindled interest in the status of IMNs. The rate of drainage to IMN tends to reflect the method of lymphoscintigraphy. High rates of IMN mapping success have been attributed to ultrasound-guided peritumoral injection with 99mTc-antimony sulfide colloid radiopharmaceutical.<sup>8</sup> Two important determinants of detection of IMN drainage are the radiocolloid particle size and the site of radiocolloid injection in the breast: deep peritumoral injections require small-particle colloids because large-particle radiocolloids do not migrate well from the injection site.<sup>8</sup> When small-particle radiocolloids are not

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Table 1  
Assumptions used in the models.

Assumption	Definition
1	Lymphatic drainage patterns visible on lymphoscintigraphy after peritumoral radiocolloid injections are a true reflection of lymphatic drainage anatomy of the tumor.
2	Lymphoscintigraphy will identify all sentinel metastasis from a breast cancer to a nodal group (e.g. internal mammary and axillary) and when lymphatic mapping does not identify any of the nodes within the group as sentinel nodes, the remaining lymph nodes in that area are all assumed to be negative.
3	The rate of metastasis to a lymph-node group (internal mammary or axillary) is equivalent to the rate of sentinel node mapping multiplied by the rate of positive sentinel lymph nodes in the node group. This assumption is made for each T (primary tumor) stage or overall rates, i.e: Rate of nodal metastasis = rate of sentinel node mapping x rate of positive sentinel LNs
4	The probability of breast cancer metastasis to a lymph node is a reflection of the intrinsic tumor biology and lymphatic anatomy. Lymphatic anatomy is assumed to be constant in a large population analysis and over time. Hence the ratio of lymphatic channels between internal-mammary and axillary-lymph-nodes would be constant, similarly metastasis. In addition breast cancer biology has been constant over time with the exception of earlier diagnosis. So we assume the tendency for breast cancer in a population study to metastasize to the IMN will follow a similar trend and ratio to that of axillary lymph nodes depending on tumor biology (e.g. T stage) and lymphatic anatomy (lymphoscintigraphy).

available, the breast injections have been given superficially into the dermis or in the peri-areolar area, radiolabeling an axillary sentinel node. As explained by recent anatomic studies by Suami et al.<sup>9</sup> and lymphoscintigraphy observations<sup>10</sup> superficial sites rarely drain to nodes outside the axilla. Ultrasound-guided peritumoral lymphoscintigraphy (draining via the perforating lymphatic system) have a higher rate of IMN drainage than subareolar or subdermal (superficial lymphatic system) injections. Also, a peritumoral injection more accurately demonstrates the true lymphatic drainage of the tumor than an injection given away from the tumor site in the skin or around the areola. Because of these issues, the reported rates of IMN drainage on lymphoscintigraphy vary greatly, from <2% to 38% of all breast tumors.<sup>8,11,12</sup>

The rate of visualization of sentinel IMN seems to be the principal determinant of whether surgeons are advocates of transpectoral IMN biopsy. Infrequent opportunity to do IMN biopsy in most breast surgeons' settings can lead to lack of conviction that it is of value. Many breast surgeons, due to the lack of technical expertise and familiarity with the route of access, have concerns about the rate of complications of the procedure. Furthermore, many authors have questioned the value of IMN biopsy in the era of earlier breast cancer diagnosis, when most decisions on systemic therapy are increasingly made on primary tumor characteristics and gene profiling. However the status of IMN in determining radiotherapy fields is controversial as well with significant institutional bias on the indications for this. A large EORTC trial on this subject is yet to be reported. Other trials on radiotherapy have had issues of selection bias and none of these trials have used IMN lymphatic drainage on lymphoscintigraphy as a method of selecting patients for treatment.

We contend from our experience IMN metastasis alters the introduction and escalation of chemotherapy regimens in many patients, and the introduction of focused IMN/supraclavicular and chest wall radiotherapy in all patients

as this is not routinely delivered.<sup>13,12</sup> Improvement in locoregional and systemic adjuvant therapy can impact on survival as demonstrated by the Milan and Dutch experience.<sup>14,15</sup> In addition, accurate staging with knowledge of the IMN lymphatic mapping and histological status can accurately tailor adjuvant therapy reducing unnecessary IMN irradiation practiced in some centres based on primary tumor characteristics.

In the absence of clinical trial evidence we have derived a method to estimate contemporary rates of IMN metastasis to assist clinicians making therapeutic decisions on systemic and locoregional adjuvant therapy. This method is based on mathematical modeling using available historical and contemporary datasets.

## Methods

The anatomical and tumor biology assumptions necessary to accept this modeling are stated in Table 1.

The modeling involved integration of the following 3 areas of derived data.

1. Historical summary data on multiple ERM series published by Bevilacqua et al.<sup>16,1,17–23</sup> [1 17–23] are used to derive predicted rates of IMN metastases in contemporary patients. In addition a separate analysis of an individual ERM database of 1,295 patients (Shimazu et al.) was performed to determine the relationship of IMN metastasis with depth of tumor location.<sup>11</sup>
2. A current high resolution peritumoral lymphoscintigraphy series is used to define breast lymphatic anatomy and hence rates of IMN drainage from the different sectorial locations within the breast.
3. The SEER database was used to define rates of axillary node positivity in a contemporary sentinel node era population.

## Results

### Historical data

The rate of IMN metastases in the combined analysis by Bevilaqua et al. of the ERM series not biased by overrepresentation of medial tumors gave an overall rate of 18.7%. The patients included had an axillary node positivity (AN<sup>+</sup>) rate of 48.6%. Thus there was a ratio of  $18.7/48.6 = 0.385$  which equates to the relative chance of lymph node positivity in the 2 groups of lymph nodes. When the AN<sup>+</sup> subgroup was assessed alone, 31.1% had positive IMN. The axillary node negative (AN<sup>-</sup>) subgroup had an IMN<sup>+</sup> rate of 6.7%.

### Lymphoscintigraphy data

Anatomical data was implied from consecutive series of breast lymphoscintigraphies from the co-authors (RFU) nuclear medicine practice.<sup>12</sup> From October 1992 to May 2007, of the 1754 patients underwent breast lymphoscintigraphy using techniques described, ultrasound-guided peritumoural injections of 99mTc-antimony sulfide colloid radiopharmaceutical.<sup>8</sup> 1675 showed drainage to the axilla, and 594 patients had sentinel IMNs identified (Table 2). Only 48 patients did not show tumor drainage to either node group. The rate of IMN mapping from medial tumors was 52.7%, central 37.8%, and lateral 24.4%. The rates of IMN sentinel node identification and axillary sentinel node identification in the data presented in Table 2 overall is  $33.9/95.5 = 0.36$ .

Table 2  
Lymphatic mapping from different breast sectors (%).<sup>a</sup>

Sectors	n	IMNmap <sup>+</sup> %	ANmap <sup>+</sup> %	Ratio IMNmap <sup>+</sup> :ANmap <sup>+</sup> per sector <sup>b</sup>	Adjustment Coefficient for Modeling <sup>c</sup>
Upper Inner Sector (UIS)	247	53%	88%	0.60	1.7
Upper Lower Inner Sector (ULIS)	62	60%	94%	0.64	1.8
Lower Inner Sector (LIS)	97	47%	93%	0.51	1.4
Medial (UIS + ULIS + LIS)	406	53%	90%	0.58	1.6
Upper Inner Outer Sector (UIOS)	241	36%	96%	0.37	1.0
Nipple (N)	61	33%	93%	0.35	1.0
Lower Outer Inner Sector (LOIS)	92	47%	98%	0.48	1.3
Central (UIOS + N+LOIS)	394	38%	96%	0.39	1.1
Upper Outer Sector (UOS)	610	18%	97%	0.19	0.5
Upper Lower Outer Sector (ULOS)	183	29%	98%	0.30	0.8
Lower Outer Sector (LOS)	150	43%	100%	0.43	1.2
Lateral (UOS + ULOS + LOS)	943	24%	98%	0.25	0.7
Total (All sectors)	1743	34%	96%	0.36	

<sup>a</sup> Source: Breast lymphoscintigraphy series from one of the authors (RFU). Data simplified to integer values. 11 patients had no information on tumor location in the database.

<sup>b</sup> This value is the ratio of individual IMN lymphatic mapping to AN lymphatic mapping in each given sector.

<sup>c</sup> This adjustment coefficient is derived from the ratio of individual sector IMN:AN ratios to the overall Adjustment Coefficient =  $\frac{\text{Ratio IMNmap}^+:\text{ANmap}^+ \text{ for an individual sector}}{\text{Ratio IMNmap}^+:\text{ANmap}^+ \text{ overall (all sectors)}}$ .

### SEER data on rates of axillary metastasis

The third source of information was the SEER registries, comprising 14 regional registries known to be of high quality and available online. The registries include 669 083 breast cancer cases (1973–2004), of which 201 680 were diagnosed between the years 2000 and 2003. The cases analyzed were limited to female patients with staging information available. Only cases coded for stages equivalent to T1–T3 and AN<sup>+</sup> were analyzed (coded as extent of disease, 10–38, and N1–N6). The rates of AN metastasis over 4 years (2000–2003) with variation of tumor size were derived (Table 3 and Fig. 1).

### Biological and mathematical modeling

*Establishing models based on assumptions on breast lymphatic anatomy.* The first assumption defines that lymphatic drainage patterns visible on lymphoscintigraphy are a clear reflection of the lymphatic drainage anatomy of the tumor. This leads on to the second assumption that lymphoscintigraphy will identify all sentinel node metastasis from breast cancer. When lymphatic mapping does not identify any nodes within a nodal group (IMN or AN) as sentinel then the remaining nodes in the area are assumed to be negative.

Derived from these assumptions, the third assumption mathematically equates the probability (rate) of nodal metastasis as equivalent to the probability of sentinel node mapping multiplied by the probability of positive sentinel

Table 3  
Rate of axillary lymph-node metastasis (SEER Registry 2000–2003)<sup>a</sup> and prediction of internal mammary lymph-node metastasis according to tumor size and stage.

From SEER registries <sup>a</sup>	Predicted rates of nodal metastasis: (%)								
	Tumor size (mm)	All tumors n	AN <sup>-</sup> %	AN <sup>+</sup> %	IMN metastasis <sup>b,f</sup>	Positive Sentinel (IMN or AN) Nodes <sup>c</sup>	IMN+ in pts without AN metastasis <sup>d,f</sup>	IMN+ in pts with AN metastasis <sup>d,f</sup>	Positive Sentinel IMN in pts without AN metastasis <sup>e,f</sup>
T microscopic	3474	91	8.7	3.2	9.1	2.4	11	6.6	31
T1a (1–5)	10,193	92	8.3	3.1	8.7	2.4	11	6.4	30
T1b (6–10)	32,322	87	13	4.9	14	3.3	15	8.9	41
T1c (11–20)	65,247	72	28	10	30	5.1	24	14	64
T2a (21–30)	31,184	55	45	17	48	6.3	29	17	79
T2b (31–40)	11,378	45	55	20	58	6.8	32	18	85
T2c (41–50)	5,491	40	60	22	63	7.0	32	19	88
T3 (50+)	7,546	33	67	25	70	7.2	33	20	90
Total	166,835								
T average		69	31	12	31	5.6	26	16	72

<sup>a</sup> Source: SEER registry database. All breast cancer limited to locoregional disease with available information on AN status in SEER database (Period: 2000–2003; coded as extent of disease 10–38, N 0 and 1–6). Data simplified to integer values except for single digit calculations.

<sup>b</sup> Derived overall rate of IMN metastasis in relation to tumor size and irrespective of tumor position, lymphoscintigraphy status and axillary status. [=0.37 x rate of AN<sup>+</sup>].

<sup>c</sup> Derived rate of positive sentinel nodes pertain to either nodal basin (AN or IMN) and derived from assumptions 3 and models 1 & 2.

<sup>d</sup> Derived rates of IMN metastasis in patients where information on tumor size and axillary status (with or without metastasis) is available. Lymphoscintigraphy data is not available or unreliable regarding IMN status.

<sup>e</sup> Derived rates of Sentinel IMN metastasis in patients where information on tumor size and axillary status (with or without metastasis) is available, i.e. the probability of IMN metastasis if high quality peri-tumoral lymphoscintigraphy demonstrates IMN mapping in patients where tumor size and axillary status is available.

<sup>f</sup> To adjust the impact on the rate of IMN metastasis for tumor position within different breast sectors and depth, adjustment coefficients were derived. To adjust for individual sectors of the breast a coefficient listed in Table 2, column 6 needs to be multiplied. For example x1.7 for UIS lesions. In addition a large retrospective ERM database (Shimazu et al.) was analysed to model an adjustment coefficient for superficial and deep lesions. Superficial and deep lesions had IMN+/AN+ ratios of 0.31 and 0.37 respectively, giving adjustment coefficients of 0.9 and 1.1 respectively.

nodes in the group. Similarly, a fourth assumption defines the probability (rate) of breast cancer to metastasize to a lymph node is solely a reflection of the intrinsic tumor biology and lymphatic anatomy. We assume that all regional nodes have similar capacity to retain metastasis. Therefore the chance of sentinel node positivity at any site (axillary or extra-axillary) is dependent on tumor biological metastatic potential, i.e. related to size, grade and LVI and the anatomical pattern of lymphatic drainage.

Clearly in a large population analysis, all women would have lymphatic anatomy that is constant over the generations and time. Thus, in large dataset analyses:

Ratio of IMN:AN mapping = Ratio of IMN:AN metastasis = Constant factor

Or more simply stated: The Rate of Positive Sentinel IMN = Rate of Positive Sentinel AN

As stated above the historical ratio is 0.385.

Thus the contemporary ratio should remain constant. The predicted numerator (IMN) and denominator (AN) for this ratio will vary in a contemporary population as the rate of axillary node positivity is lower. Utilising this ratio, the SEER data has been modeled to demonstrate a nomogram for contemporary IMN positivity rates with respect to tumor size and axillary stage (Fig. 1). This is done by using a reducing ratio (or stage migration) of

historical axillary node positivity rate to contemporary mean tumor size axillary node positivity rate from the SEER data (i.e. 48.6/31.3). Similarly, historical ratios for IMN positivity in AN+ and AN– subgroups were modeled on the SEER data (Fig. 1). This data is also represented in simple numerical form in Table 3 and can be used as a nomogram in cases where lymphatic mapping is inferior to that cited or where IMN biopsy was unsuccessful or not performed.

Notably these relationships derived from the lymphatic mapping data and historical stage migration data are very similar providing validation to the accuracy of the lymphatic mapping database and models. For simplicity of further modeling this relationship is taken as 0.37. From this relationship simplified models are derived:

- a. Rate of IMN metastasis ~ 37% Rate of AN metastasis
- b. Rate of IMN metastasis ~ 37% Rate of IMN mapping

Given the average rate of AN mapping is 96%, then:

- c. Rate of Sentinel node (AN or IMN) metastasis = 1.05 Rate of AN metastasis
- d. Rate of IMN metastasis ~ 39% Rate of positive Sentinel AN

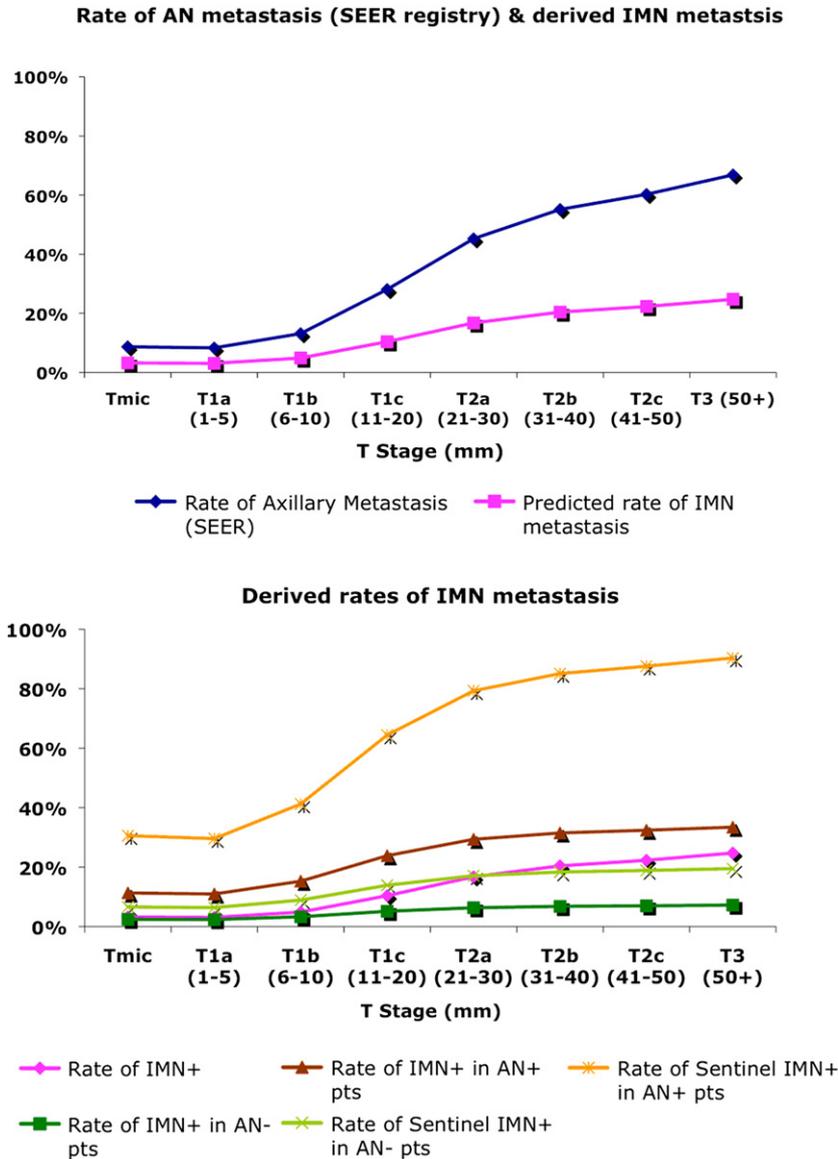


Figure 1. Rates of lymph-node metastasis according to tumor size. The dark blue line is the established rates of axillary node metastasis with respect to tumor size (SEER registry). The purple line demonstrates predicted rates of internal mammary lymph-node metastasis in relation to tumor size. The other lines show estimated rates of metastasis in relation to tumor size and axillary stage calculated from historical data and contemporary databases. See Table 3. SEER = Surveillance Epidemiology and End Results registries; AN = axillary lymph nodes; IMN = internal mammary lymph nodes.

These relationships apply for a large population analysis and can be adjusted for different tumor stages and quadrants and depth location within the breast. Modeling can be used to determine these adjustment factors to further refine predictions and are summarized in Table 3 and 4.

**Discussion**

High rates of IMN mapping are a reflection of deep peritumoral injections and the use of 99mTc-antimony sulfide colloid radiopharmaceutical. These rates were relatively consistent in the database previously published.<sup>8,12</sup> In addition, similar high rates of IMN lymphatic mapping have been reproduced in a separate unrelated institution using the

same lymphatic mapping methods.<sup>12</sup> Despite high rates of IMN mapping, our rates of positive sentinel IMN (18–20%) are comparable to those published,<sup>12</sup> providing evidence of validity. Evidence in the form of modeling demonstrates the ratios of IMN:AN mapping should approach historic IMN:AN metastasis ratios of 0.38 with predicted contemporary rates of IMN metastasis at approximately 12%.

Through modeling based on historic ERM and SEER data, we have derived estimates of the frequency of IMN metastasis with variation in tumor size, location and axillary stage (Table 3 and Figure 1). Similarly simplified predictive models that are versatile can be used as an adjunct to current axillary nomograms and treatment algorithms. Although these models may be difficult to validate, as

Table 4  
Derived models for clinicians.

1. Rate of positive Sentinel IMN  $\sim$  Rate of positive Sentinel AN<sup>a</sup>
2. Rate of Sentinel node (IMN or AN) metastasis = 1.05 Rate of AN metastasis<sup>b</sup>
3. Rate of IMN metastasis  $\sim$  37% Rate of IMN mapping<sup>a</sup>
4. Rate of IMN metastasis  $\sim$  37% Rate of AN metastasis<sup>a</sup>
5. Rate of IMN metastasis  $\sim$  39% Rate of positive Sentinel AN<sup>a</sup>

<sup>a</sup> This would apply for all tumor locations and T stages.

<sup>b</sup> These models would reflect relationships for all tumors in a population analysis. To adjust for individual positions/sectors a multiplication coefficient listed in Table 2 (column 6) needs to be applied. For example  $\times 1.7$  for upper-inner sector (UIS) lesions. Similarly for superficial and deep lesions a coefficient of 0.9 and 1.1 respectively needs to be multiplied (refer to footnote f in Table 3). These adjustments are valid for models 2–5.

full IMN dissection is not practiced, the assumptions and calculations are sound. The two situations where these models could be utilized are:

1. In a center utilizing high quality lymphoscintigraphy with demonstrated high frequency of IMN mapping (ranging from 33 to 37% or IMN:AN mapping ratios of  $\sim 0.37$ ) this information can be readily coupled with available nomograms predicting positive Sentinel ANs based on primary tumor characteristics.<sup>24</sup> One can predict the probability of sentinel IMN metastasis to equal that of axillary sentinel node metastasis status (model 1) if both nodal basins demonstrate lymphatic mapping. This can be determined on the basis of primary tumor characteristics solely irrespective of tumor position based on the assumptions and models.

For example, utilizing derived information from SEER registries (Table 3) the probability of positive sentinel node (AN or IMN) for a patient with a 9 mm cancer will be  $\sim 14\%$  (Table 3, column 6). If the status of the axilla has been determined as positive, then for the same patient with a 9 mm cancer that demonstrated IMN mapping and was not biopsied there is a  $\sim 41\%$  probability of the IMN being positive (Table 3, column 10). Similarly if the AN status was negative this drops to  $\sim 9\%$ . Hence, one can use columns 6, 9 and 10 in Table 3 to predict IMN status given tumor size, AN status and high definition peritumoral lymphoscintigraphy. Variation for tumor position and depth can be made using the ratios in the footnotes of that table.

As demonstrated once AN status has been determined positive, if the IMN mapping was positive, the likelihood of them harboring metastasis is very high (Table 3, column 10). Such large variation in IMN metastatic rate may have a significant impact on adjuvant therapy decisions.

2. In a center where IMN mapping is less than ideal, all IMN that are mapped should have an attempted biopsy. If positive, treatment can be initiated with confidence. If negative, this could be a false negative arising from an error in the mapping or surgical technique. In such a situation, model 4 or 5 (Table 4)

adjusted for tumor location can be coupled with existing nomograms predicting axillary status.<sup>24</sup> Alternatively, SEER based modeling to predict nodal status with adjustment co-efficients for tumor positions (Table 3, columns 4, 5, 6 and footnote f)

Predictive models and nomograms are increasingly used as decision aids in planning adjuvant therapy. For example, nomograms are available to assist with recommendations for post-mastectomy radiotherapy.<sup>25</sup> Validation of the proposed IMN models would be difficult. It could be done if a large cohort of patients underwent concurrent accurate trans-pectoral IMN sentinel node localization and biopsy followed by an IMN dissection, as in axillary dissection with axillary sentinel node validation. IMN dissection would only be accepted by patients today if it were performed thoracoscopically with minimal morbidity which has been described.<sup>26</sup> Alternatively, if large historic extended radical mastectomy datasets were collated and analysed in greater detail, one may accurately correlate tumor characteristics and axillary staging with IMN staging.

Underpinning the modeling are several logical assumptions outlined in Table 1. Although some of these are untested and do not account for statistical and test error, the principles are intuitively sound. In the first 2 assumptions, we needed to assume that the high definition lymphoscintigraphy accurately maps nodal drainage of the breast cancer and is a true reflection of lymphatic anatomy. This has long been considered a reasonable assumption for the axilla where the vast majority of patients have lymphatic drainage. However, IMN mapping results are widely disparate (2–38%) casting doubt on the quality of lymphatic mapping and its accuracy to delineate anatomy.<sup>12</sup> As demonstrated the lymphoscintigraphy database used in these models reflect the ratios of IMN to axillary metastasis demonstrated in historic datasets providing some validity to the assumptions and modeling. Similarly, the tendency for breast cancer to metastasize to nodes is a reflection on tumor biology and lymphatic anatomy. If lymphatic anatomy is accurately delineated by lymphoscintigraphy then tumor biology is reflected by the rate of positive sentinel lymph nodes.

It is logical and highly probable that over generations breast lymphatic anatomy would remain constant with similar ratios of lymphatic density to both nodal groups. If lymphatic anatomy is constant then we argue the ratios of lymphatic mapping to positive sentinel nodes and nodal metastasis should be similar. If the predictive models hold true, an explanation to account for low rates of positive sentinel IMN compared with sentinel AN in the literature could be due to a high false-negative rates in the IMN mapping and biopsy technique.

Internal mammary Sentinel node evaluation is a procedure in its infancy. The large variation of IMN mapping rates add concern that the whole utility may have high false-negative rates. It is essential that this technique be adequately scrutinized, as predictably a large number of breast cancer patients have IMN metastasis (overall 12%).

The findings of positive IMN does influence adjuvant therapy decisions,<sup>13,12</sup> which can impact on survival as demonstrated by the Milan and Dutch experience.<sup>14,15</sup>

## Conclusion

Models provided can be the basis of a nomogram to assist decision algorithms if high quality peritumoral lymphoscintigraphy is unavailable.

## Conflict of interest

The authors declare that they have no conflict of interest.

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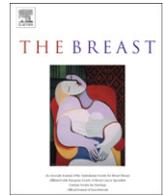
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## **CHAPTER 5:**

**Internal mammary lymph node metastasis in breast cancer:  
Predictive models to assist with prognostic influence.**



## Original article

## Internal mammary lymph node metastasis in breast cancer: Predictive models to assist with prognostic influence

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## ABSTRACT

**Background:** Metastatic breast cancer in the internal mammary nodes (IMN) indicates a poor prognosis. Several recent epidemiological surveys have determined a reduction in survival for patients with medial compared to lateral sector tumors attributing this to a higher rate of unrecognized IMN metastasis and hence these patients are undertreated with adjuvant therapy.<sup>1–6</sup>

**Aim:** Through mathematical modeling based on large datasets we aim to quantify the impact on survival of IMN metastases at different tumor and axillary stages.

**Methods:** Mathematical models were created to estimate the survival of patients with and without IMN metastasis. It was assumed that the different rate of survival between medial and lateral sector breast cancers was a result of the differential rate of unrecognized IMN metastases with resultant under-staging and under treatment. We applied these models on a retrospective database analysis from the Surveillance, Epidemiology and End-Results (SEER) registries from 1994 to 2003.

**Results:** The 10-year odds of death (OOD) from breast cancer for patients with medial compared with lateral sector tumors ranged from 1.2 to 1.5 depending on stage. The predicted odds of breast cancer death for patients with unrecognized IMN metastases ranged from 2.4 to 20, with the highest OOD in the groups with small tumors and no axillary node metastasis.

**Conclusions:** Through modeling we have been able to predict and quantify the significantly worse survival outcomes for patients with undiagnosed IMN metastasis.

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## Introduction

There is evidence over a number of decades that metastatic breast cancer in the internal mammary nodes (IMN) indicates poor prognosis and is of similar prognostic importance as axillary lymph node involvement.<sup>7–18</sup> In these studies overall survival outcome is nearly twice as bad if metastases were present in both axillary and internal mammary nodal basins. In contemporary populations several studies describe a reduction in survival of patients with medial compared with lateral sector tumors and have attributed this to a higher rate of undetected and undertreated IMN metastases from medial sector tumors.<sup>1–6</sup> Although the reduction in survival for patients with medial tumors is thought to be significant, the true impact of IMN

metastasis on survival has not been evaluated in the contemporary setting. A recent retrospective analysis has demonstrated that tumors that have IMN mapping on lymphoscintigraphy alone have a worse prognosis, even though these nodes were not biopsied.<sup>19</sup>

Establishing the IMN nodal status by pathological examination is the gold standard for tumor staging. The resultant enhancement of accuracy of staging results in appropriately tailored adjuvant therapy, which would result in an improvement in survival. This outcome is implied by two recently published studies in European centers that regularly biopsy internal mammary nodes.<sup>20,21</sup>

However due to a number of reasons, including the technique of lymphatic mapping used,<sup>22</sup> many surgeons choose not to evaluate the IMNs. In theory this may potentially compromise the survival outcome of these patients. The authors have recently published mathematical models and algorithms to estimate the rate of IMN metastasis to assist in adjuvant therapy planning in such situations.<sup>23</sup> To expand on this we sought to estimate the quantum of diminished survival IMN metastasis confers to help persuade

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colleagues of the importance of accurate IM nodal staging. In contrast there is much interest in the micro-evaluation of axillary nodes to determine their impact on staging and survival, yet little attention is paid to the status of the IMNs.

## Methods

In our previous publication four biologically plausible assumptions and associated models were created to estimate the rate of IMN metastasis (Tables 1 and 2).<sup>23</sup> To model for survival impact a fifth assumption was made that the sole reason for the diminished survival in medial versus lateral sector breast tumors is due to a greater rate of undiagnosed and undertreated IMN metastasis in medial sector tumors. Using this assumption and the previous predicted rates of IMN metastasis, one can mathematically quantify the impact on survival that these metastases confer.

To achieve this a retrospective data analysis was performed on the Surveillance, Epidemiology and End-Results (SEER) registries to ascertain the impact of tumor location within the breast on breast-cancer-specific survival in the United States similar to previously done, but updating the results of Gaffney et al.<sup>3</sup> The SEER database (1973–2004) includes 669,083 breast cancers, of which 349,806 were diagnosed between the years 1994 and 2003. The analysis was limited to female patients with available information on tumor location, axillary and tumor staging equivalent to T1–T3 (SEER modified AJCC 3rd edition: coded as extent of disease 10–38 and N 0 or 1–6). There were no limitations made on the data with respect to the type of surgery and adjuvant therapy. The SEER program was run to estimate 10-year breast-cancer-specific survival in the 10-year cohort of patients (1994–2003) for a given tumor size and axillary stage. Kaplan–Meier statistical analysis was performed with available on-line SEER software to determine breast-cancer-specific survival and standard error. In the interests of brevity only results with a significant difference between medial and lateral sector cancers were further presented. Estimated 10-year survival

of patients with medial (upper-inner and lower-inner quadrants), lateral (upper-outer, lower-outer quadrants and axillary tail) sector tumors and overall survival was extracted for use in the predictive model.

In addition utilizing results from previous modeling<sup>23</sup> we were able to estimate the frequency of IMN metastasis (Table 2).

We constructed a model to determine the survival impact undiagnosed IMN metastasis conferred:

### *Modeling to estimate the survival of patients with positive internal mammary nodes*

Based on assumption 5 and previous models (Table 1) we expanded the modeling to determine the survival impact of undetected and undertreated IMN metastasis (Fig. 3). Utilizing equations (4) and (5) coupled with rates of IMN metastasis (Q) previously estimated (Table 2)<sup>23</sup> and current SEER rates of medial (M) and lateral (L) sector breast-cancer-specific survival (Table 3) one can estimate the survival of patients with untreated IMN metastasis.

## Results

Significant survival difference between medial and lateral sector cancers was evident only for the tumor size (T) stages listed (Table 3). These results were analyzed further with modeling described and results are presented in Figs. 1 and 2. Survival modeling of patients with and without IMN metastasis has demonstrated a significant difference in mortality at 10 years follow-up, which is more significant for AN negative patients. Patients without AN metastases and tumors ranging from 11 mm to 30 mm would have a predicted increase in mortality (odds of death) ranging from 20-fold to 7.1-fold if they were to have IMN metastasis. Similarly, patients with AN and IMN metastasis and tumors ranging from 6 mm to 40 mm would have a predicted increase in mortality ranging from 6.2-fold to 2.4-fold (Table 3, Figs. 1 and 2).

**Table 1**  
Assumptions used in the models.<sup>a</sup>

Assumption	Definition	Supportive evidence for assumptions
1	Lymphatic drainage patterns visible on lymphoscintigraphy after peritumoral radiocolloid injections are a true reflection of lymphatic drainage anatomy of the tumor.	Basic assumption of sentinel node technology. This has been validated by the early studies on completion axillary dissection after sentinel node biopsy. <sup>26</sup> Anatomical models of Suami et al. supportive of this assumption. <sup>27</sup>
2	Lymphoscintigraphy will identify all sentinel metastasis from a breast cancer to a nodal group (e.g. internal mammary and axillary) and when lymphatic mapping does not identify any of the nodes within the group as sentinel nodes, the remaining lymph nodes in that area are all assumed to be negative.	Idealised logical extension of assumption 1. Does not account for false negativity in sentinel lymph node technology.
3	The rate of metastasis to a lymph node group (IM or axillary) is equivalent to the rate of sentinel node mapping multiplied by the rate of positive sentinel lymph nodes in the node group. This assumption is made for each T (primary tumor) stage or overall rates, i.e.: Rate of nodal metastasis = rate of sentinel node mapping × rate of positive sentinel LNs ( $Q = U \times R$ )	Derived model based these simple calculations.
4	The probability of breast cancer metastasis to a lymph node is a reflection of the intrinsic tumor biology and lymphatic anatomy. Lymphatic anatomy is assumed to be constant in a large population analysis and over time. Hence the ratio of lymphatic channels between IMN and axillary LN would be constant. In addition breast cancer biology has been constant over time with the exception of earlier diagnosis. So we assume the tendency for breast cancer in a population study to metastasize to the IMN will follow a similar trend and ratio to that of axillary lymph nodes depending on tumor biology (e.g. T stage) and lymphatic anatomy (lymphoscintigraphy).	Ratios of IMN to axillary LN metastasis have been established in old extended radical mastectomy databases ( $\sim 1/3$ ). <sup>28</sup> This ratio is similar to published analyses on 2 separate large peritumoral lymphoscintigraphy databases supporting the contention. <sup>22,23</sup>
5	The difference in survival of medial sector compared with lateral sector breast cancers is due to a greater percentage of undetected IMN metastasis in medial sectors tumors. Hence this staging information is not taken into account when planning adjuvant therapies.	Several epidemiological analyses have demonstrated this difference in survival. All authors have supported this assumption as likely cause. <sup>1–6</sup>

<sup>a</sup> Table modified from authors previous publication.<sup>22</sup>

**Table 2**  
Rate of axillary lymph node metastasis (SEER Registry 2000–2003) and prediction of internal mammary lymph node metastasis according to tumor size and stage.<sup>a</sup>

Tumor size (mm)	From SEER registries		Derived rates of IMN metastasis		
	AN <sup>-</sup> (%)	AN <sup>+</sup> (%)	Overall rate of IMN metastasis (Q) <sup>b</sup> (%)	Rate of IMN+ in pts without AN metastasis <sup>c</sup> (%)	Rate of IMN+ in pts with AN metastasis <sup>c</sup> (%)
T1a (1–5)	92	8.3	3.1	2.4	11
T1b (6–10)	87	13	4.9	3.3	15
T1c (11–20)	72	28	10	5.1	24
T2a (21–30)	55	45	17	6.3	29
T2b (31–40)	45	55	20	6.8	32
T2c (41–50)	40	60	22	7.0	32
T3 (50+)	33	67	25	7.2	33

<sup>a</sup> Table modified from authors previous publication.<sup>22</sup> All breast cancer limited to loco-regional disease with available information on AN status in SEER database (Period: 2000–2003; coded as extent of disease 10–38, N 0 and 1–6). Data simplified to integer values except for single digit calculations.

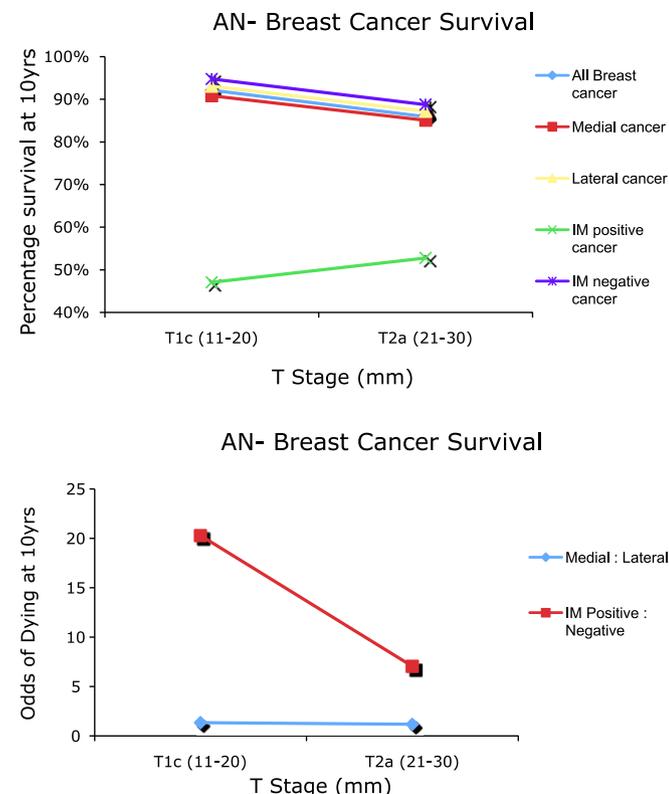
<sup>b</sup> Derived overall rate of IMN metastasis (Q) in relation to tumor size and irrespective of tumor position, lymphoscintigraphy status and axillary status.

<sup>c</sup> Derived rates of IMN metastasis in patients where information on tumor size and axillary status (with or without metastasis) is available.

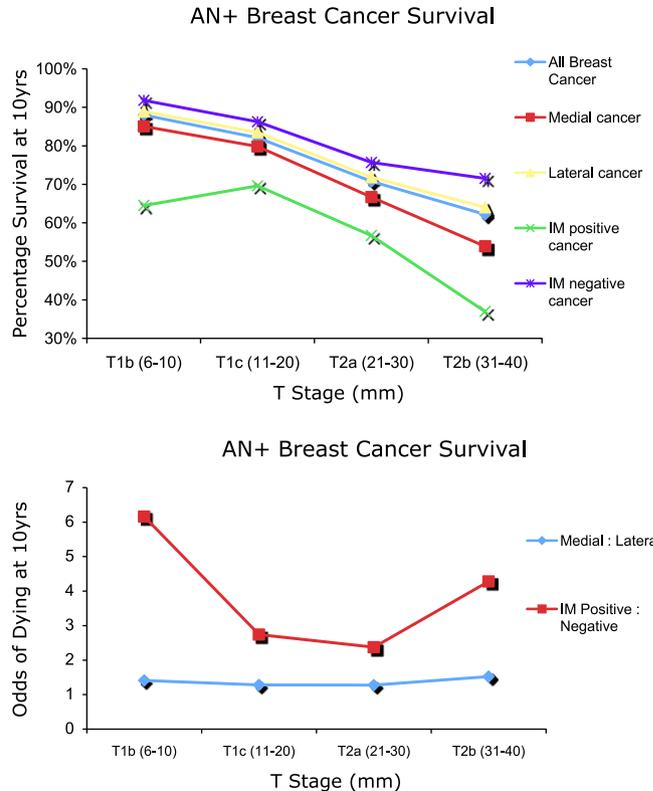
**Discussion**

*Relevance of IMN staging*

As long as there is a requirement to stage the axilla one cannot ignore the validity of IM sentinel node biopsy. However increasingly in the era of molecular classification and targeted therapies one may argue the need for accurate nodal staging. Yet the vast majority of oncologists globally continue to base their breast cancer management on pathological and TNM staging. Decades of



**Fig. 1.** Predicted survival at 10 years and odds of dying, for patients with no axillary lymph node metastasis.



**Fig. 2.** Predicted survival at 10 years and odds of dying, for patients with axillary lymph node metastasis.

evidence have established the necessity of good loco-regional therapies leading to improved long-term survival. The most compelling support of local therapies has been the overview of randomized trials performed by the Early Breast Cancer Trialists' Collaborative Group. Here they highlight the significant impact on long-term survival (>15 years) in patients who had loco-regional recurrence.<sup>24</sup>

The recent outcome of the NSABP-32 trial is reassuring that sentinel node biopsy is accurate in staging patients and the few who are missed do not come to any harm.<sup>25</sup> However on further interpretation one could suppose that the vast majority of patients received good local therapy with whole breast radiotherapy (82%) or adjuvant systemic therapy (84%). It is well known that post-operative radiotherapy treats axillary nodes helping to reduce local recurrence,<sup>26</sup> similarly it would be logical to assume this would also benefit patients with IMN metastasis if targeted radiotherapy was provided.

*Incidence of IMN recurrences*

Great deal of scepticism surrounds the benefit of IMN evaluation principally due to apparent low rates of IMN recurrence. Due to the size and position of these nodes, metastasis may never become clinically apparent. As these nodes are very small (3–4 mm) even with tripling in their size they may not be detected by routine imaging. It is highly probable that IMN metastasis may only manifest as pleural, pulmonary or sternal disease due to local invasion, which is common. It is also logical to assume that an untreated nidus of disease in a regional lymph node can progress to metastatic disease and this may explain why medial tumors, with higher rates of IMN metastasis, have a poorer outcome. There is

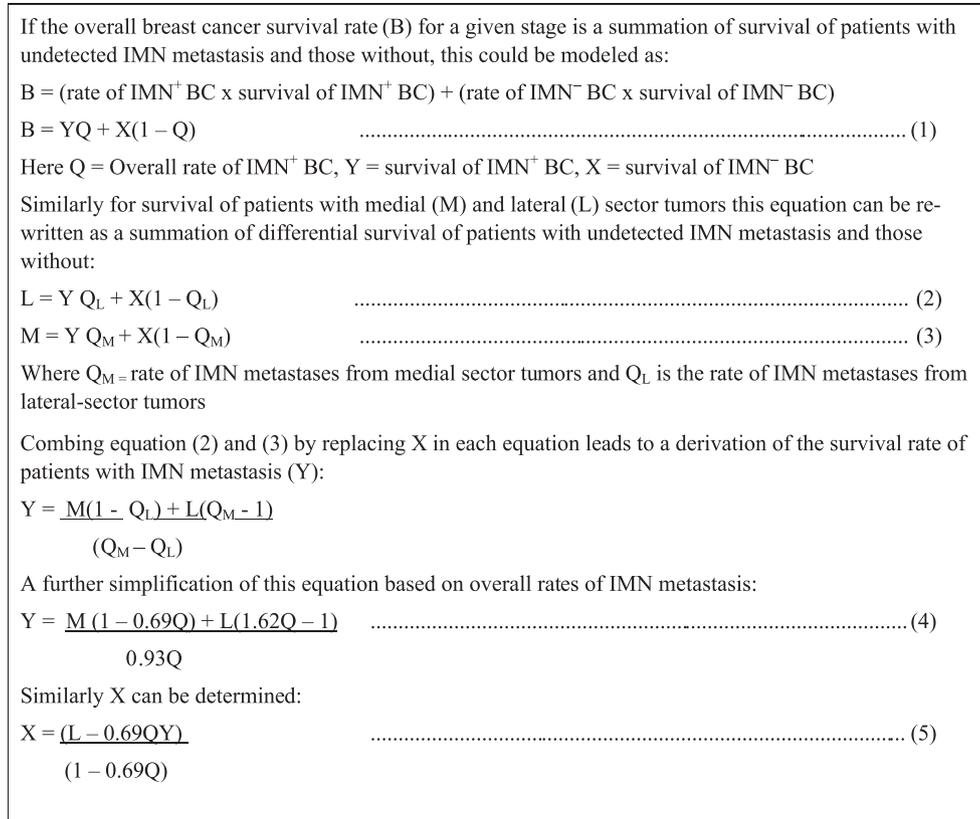


Fig. 3. Mathematical modeling of survival of patients with IMN metastasis (Y).

abundant literature on the rates of IMN metastasis in early breast cancer, however the vast majority is identified on surgical biopsy.

Improvements in imaging technology may well lead to increasing non-operative recognition of IMN involvement with

disease. A significant publication from the MD Anderson group retrospectively analyzed their imaging data (2000–2006) and determined on imaging alone (principally high resolution ultrasound) detected a 14% involvement of these nodes in patients with

**Table 3**  
Predicted survival at 10 years, derived from the SEER database, 1994–2003.

Tumor size & axillary node stage	From SEER Registry					Odds ratio of M:L BCSS	p-value	Derived from modeling <sup>a</sup>		
	All tumors	Medial & Lateral tumors	All Breast-cancer-specific survival (BCSS)	Medial sector BCSS (M)	Lateral sector BCSS (L)			p-value	IMN metastasis BCSS (Y)	IMN negative BCSS (X)
	n	n	%	%	%			%	%	
<b>Axillary node negative</b>										
T1 Microinvasion	4470	2493	96.2	96.9	96.4	0.9	0.628			
T1a (1–5 mm)	11,648	6971	96.7	97.0	97.7	1.3	0.076			
T1b (6–10 mm)	39,582	24,982	95.9	95.8	95.7	1.0	0.566			
T1c (11–20 mm)	68,610	43,169	92.1	90.8	93.1	1.4	<0.001	47.1	94.7	20.3
T2a (21–30 mm)	25,632	15,751	85.9	85.1	87.2	1.2	<0.001	52.8	88.7	7.1
T2b (31–40 mm)	7649	4450	80.7	81.4	83.1	1.1	0.171			
T2c (41–50 mm)	3199	1805	80.0	80.3	78.1	0.9	0.315			
T3+ (50 mm+)	3600	1777	80.8	81.6	84.5	1.2	0.166			
<b>Axillary node positive</b>										
T1 Microinvasion <sup>b</sup>	418	199	85.1							
T1a (1–5 mm)	1046	568	85.0	80.2	86.4	1.6	0.086			
T1b (6–10 mm)	5846	3551	88.0	85.1	88.9	1.4	0.004	64.5	91.8	6.2
T1c (11–20 mm)	26,711	16,380	82.1	79.8	83.5	1.3	<0.001	69.6	86.3	2.7
T2a (21–30 mm)	20,825	12,428	70.8	66.7	71.9	1.3	<0.001	56.7	75.7	2.4
T2b (31–40 mm)	9369	5432	62.2	53.9	64.0	1.5	<0.001	37.0	71.5	4.3
T2c (41–50 mm)	4906	2740	58.5	51.9	61.7	1.5	<0.001	36.5	70.0	3.9
T3+ (50 mm+)	7238	3480	54.8	54.8	56.9	1.1	0.35			
<b>Total</b>	<b>240,749</b>	<b>146,176</b>								

<sup>a</sup> Modeling performed for significant survival difference between medial to lateral tumors (P < 0.5).

<sup>b</sup> Further analysis not performed due to small cohort of patients and missing data.

<sup>c</sup> Odds ratio of survival of patients with and without IMN metastasis.

advanced axillary disease (N2 and 3).<sup>27</sup> In addition with targeted adjuvant therapy, principally radiotherapy, there was significant reduction/improvement in IMN disease and disease-free survival. It is reasonable to assume that ultrasound only detected large metastasis hence an underestimation of the true incidence of IMN disease. More significantly, regression of IMN metastasis with adjuvant radiotherapy would suggest that early detection of these metastasis and improved adjuvant therapies would benefit our patients.

#### *IMN staging, adjuvant therapy and survival*

Another common criticism is that IMN staging has very little impact on adjuvant therapy. From our experience all patients with identified IMN metastasis (~8% of early breast cancer patients overall) will receive targeted IMN radiotherapy, as this is not routinely administered. In addition if the total node count increases (axillary and IMN) then they may be eligible for post-mastectomy chest wall and/or supraclavicular radiotherapy. Finally chemotherapy regimens are often escalated with the increase in overall regional disease. On occasion there are situations where chemotherapy is introduced solely on the status of IMN metastasis when none was evident in the axillary nodes. Similar impact on adjuvant therapies has been reported by the Milan and Dutch experience who routinely biopsy IMN nodes.<sup>20,21</sup>

Common arguments against IMN assessment and treatment are the evaluation of old randomized trials on IMN dissection. Although these trials were under-powered and during an era prior to adjuvant therapies, their outcomes did not demonstrate a survival advantage in those who underwent surgical dissection of all IMN nodes. However it did demonstrate the impact of IMN metastasis on survival being similar to that of axillary metastasis. Clearly we do not advocate a return to this era, on the contrary minimally invasive biopsy of selected IMN Sentinel nodes is very safe and with low morbidity. As discussed these results can influence adjuvant loco-regional and systemic therapies, which in turn can impact on survival as demonstrated by the Milan, Dutch and USA (MD Anderson) experience.<sup>20,21,27</sup>

The Milan experience has shown better than predicted 5-year survival of patients with IMN metastasis after internal mammary radiotherapy and chemotherapy.<sup>20</sup> This publication has suggested the significance of targeted therapy for IMN metastasis in improving survival outcomes comparable to those without IMN metastasis. In addition a review from MD Anderson in patients with established IMN disease on imaging studies, demonstrated a significant reduction in IMN disease and disease-free survival with targeted adjuvant therapy.<sup>27</sup> Although in this analysis patients had established axillary metastasis and gross IMN disease on imaging, there was improvement evident with tailored adjuvant therapy. While we await the results of a large EORTC trial on the subject of IMN irradiation, there is growing evidence that improvement in loco-regional and systemic adjuvant therapy can impact on survival on patients with IMN metastasis.

#### *Modeling and SEER analysis*

As randomized data are not available, it is appropriate to use mathematical modeling to assess the importance of IMN metastases. The basis of this modeling is the assumption that the difference in medial versus lateral sector breast cancer survival is due to the differential rate of undetected and untreated IMN metastasis. This is a valid assumption on the basis of historical data from extended radical mastectomies that demonstrated medial sector tumors have a greater tendency for IMN metastasis, hence are associated with poorer survival.<sup>7–18</sup> Previously we have reported

that medial tumors drain to the IMN in over 52.7% of cases but lateral tumor still drain to IMN in 24.4% of cases. In comparison, medial tumors only drain to the axilla 90.2% of the time compared to lateral tumors 97.6% of the time.<sup>22</sup> As any axillary or IMN drainage would have a similar likelihood of harboring metastases, differences in survival between medial versus lateral tumors would relate to the subtle differences in the lymphatic mapping and metastatic rates. Indeed the difference between medial and lateral sector tumors in survival has been reported from several large tumor registries, including the SEER database.<sup>1–6,28</sup> We have reconfirmed that this difference still persists in a more contemporary cohort of SEER registry patients (1994–2003). As many centers in the USA do not routinely investigate and treat these IMN it is likely that this difference in survival is due to undiagnosed and untreated IMN metastases.

Survival modeling of patients with and without IMN metastasis has shown a significant increase in mortality (odds of death) at 10 years follow-up. Intuitively patients with smaller AN<sup>-</sup> and IMN<sup>+</sup> tumors have shown the largest reduction in survival versus AN<sup>-</sup> and IMN<sup>-</sup> (OR 20, estimated 10-year survival of 47% vs 97% respectively for T1c) as they would have been erroneously classified as node negative patients and not received any adjuvant therapy. It is evident that this discordance in the survival outcome between IMN<sup>+</sup> and IMN<sup>-</sup> patients diminishes as the tumor size increases (T2a) or in patients with axillary node metastasis, which probably reflects the impact of chemotherapy.

In addition as routine IMN/Supraclavicular radiotherapy is not standard of care in the USA, similar reduction in survival was predicted in patients with concurrent AN and IMN metastases as reflected in the historic extended radical mastectomy series. It is plausible with the addition of targeted radiotherapy to the IMN chain may result in further improvements in this discordance as is implied by the retrospective database analysis performed by the Dutch and Milan group.<sup>20,21</sup>

In our analysis a survival difference between medial and lateral sector cancers was evident only for the tumor stages listed. These tumor T stages are representative of most contemporary breast cancer presentations. A plausible explanation for this is the diminishing difference in rate of IMN metastasis between medial and lateral quadrants in patients with smaller and axillary node negative tumors (Table 2) requiring a larger dataset to model. Conversely the larger likelihood of IMN metastasis in axillary node positive patients provided adequate data for modeling.

#### **Conclusion**

It seems highly likely that unrecognized, untreated internal mammary node metastasis affects survival. Further evaluation of these lymph nodes would lead to changes in adjuvant therapy in a proportion of cases, which as with other forms of improved staging would trend towards an improvement in survival in the affected cohort. Through modeling we have been able to predict a significant impact on survival for patients with undiagnosed IMN metastasis recorded in the SEER registries from 1994 to 2003. These estimated survival reductions provide us with insight into the potential for improvements in outcome if IMN metastasis are reliably identified by the combination of good lymphatic mapping and sentinel node biopsy.

#### **Conflict of interest statement**

The authors declare that they have no conflict of interest.

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## **CHAPTER 6: SUMMARY & CONCLUSIONS.**

Considerable debate still remains regarding the optimal management of IMNs in breast cancer. We predict IMN metastasis occurs in 9-12% of all early breast cancers. Although randomized controlled surgical trials in the 1970s failed to show a survival benefit with dissection of these nodes during extended radical mastectomy, a procedure that included IMN dissection, they did demonstrate diminished survival of patients with IMN metastasis [1, 2]. Historically these metastases conferred a poorer prognosis of a similar magnitude to axillary metastasis.

However there is now a renewed interest in the management of IMNs with the recent release of the radiotherapy clinical trials in which demonstrate improved long-term survival with regional radiotherapy. Despite worldwide acceptance of SLNB for axillary staging this has not automatically led to recognition of IMN staging by the majority. IMN drainage on lymphoscintigraphy is more difficult to demonstrate than AN drainage and this is due to technical reasons rather than the absence of lymphatics draining to the IMN.

However there are multiple sources of data indicating that the overall rate of IMN drainage occurs in about one-third of breast cancers and this is even more common in the medial tumours. The reason for the poor visualisation of the IMN is a result of lymphoscintigraphy technique. As detailed in Chapter 3, the lymphoscintigraphy clinical trial demonstrated a significant discrepancy in the visualisation of both axillary and IMNs between two commonly utilised techniques. The most significant discordance was evident in IMN chain where the majority of patients had no nodal visualisation in any of the IMNs. This study clearly demonstrated that peri-tumoural lymphoscintigraphy was essential in determining IMN staging. This study refutes the common argument that the entire breast drains as a single ectodermal unit to the same sentinel nodes.

The smaller discordance in axillary sentinel node mapping may not become clinically significant as additional axillary lymph nodes are often harvested by surgeons to improve their overall positive node count and the effect of tangential breast radiotherapy. However the complete unawareness of IMN status will lead to inadequate staging and treatment. If the IMN chain has not been visualised, as a result of superficial lymphoscintigraphy techniques, then surgeons would not attempt an IMN biopsy as it is technically challenging for the majority. Random IMN biopsy cannot be advocated, as this would not be feasible for the majority of surgeons and the overall yield would be low.

In chapters 4 and 5 we addressed the utility of predictive nomograms and algorithms to assist with clinical decisions regarding IMN staging. As it is apparent IMN staging is difficult due to several reasons. These include difficulty with identification of involved lymph nodes on imaging, poor lymphoscintigraphy visualisation, technical difficulty of surgical access and the high rate of failure despite an attempt at surgical biopsy. As such a high false negative rate in staging is very plausible. On the other hand routine IMN irradiation of all patients will result in overtreatment and long-term side effects when predictably only 9-12% of patients have metastasis.

In chapter 4 models and algorithms were created to determine the status of IMNs ignoring information from inadequate lymphoscintigraphy. Given information on the tumour pathology, position in the breast and the axillary lymph node status, a physician can predict the likelihood of occult IMN metastasis. This information can be utilised post-operatively to tailor IMN radiotherapy to be given to patients if rates of likely IMN metastasis were higher than 15-20%. In addition we explored the option of a pre-operative predictive nomogram to determine IMN status. Utilising the established MSKCC nomogram predicting axillary nodal status, one could easily predict the likely status of IMN metastasis by factoring the tumour position within the breast with the MSKCC nomogram by multiplying the adjustment coefficient tabled (column 6, table 2, page 18) to predict the likely IMN status.

Finally in chapter 5 we were able to determine the impact of untreated IMN metastasis on survival using modelling and the SEER database. Survival modelling of patients with IMN metastasis demonstrated a significant increase in mortality (odds of death) at 10 years follow-up. Intuitively patients with smaller tumours that had no AN metastasis however had IMN metastasis showed the largest reduction in survival versus patients that had no AN or IMN metastasis (OR 20, estimated 10-year survival of 47% vs 97% respectively for T1c). These patients would have been erroneously classified as node negative and not received any adjuvant therapy. It is evident that this discordance in the survival outcome between IMN+ and IMN- patients diminishes as the tumour size increased (T2a) or in patients with AN metastasis, which probably reflects the impact of chemotherapy on regional nodes. Of note routine IMN and supra-clavicular radiotherapy was not the standard of care in the USA during the period of the SEER database review. The estimated survival reductions provide us with an insight into the potential for improvement on outcome if IMN metastases are reliably identified by the combination of good lymphatic mapping and SLNB. As such the predicted survival reduction in patients with untreated IMNs would improve significantly given regional radiotherapy.

In conclusion, the management of regional lymph nodes in early breast cancer patients remains complex. We fear the overtreatment of our patients and the unnecessary side-effects that they may face. Conversely we do not want to miss the potential gains that loco-regional therapy has to offer. One needs to be circumspect in the analysis of the potential gains reported on regional therapy with the risk of swinging the pendulum back to the Halsteadian era where instead of aggressive surgery we now advise aggressive radiotherapy. We need to provide patients with better predictive tools to determine benefits of regional therapy. Predictive nomograms for IMN metastasis are an example that can be used to assist patients with deciding on regional radiotherapy, particularly for left sided cancers where cardiac toxicity for IMN radiotherapy would be the highest. No doubt with further analyses of all regional radiation therapy trials coupled with basic scientific research on radiosensitivity genomic signatures [14] [15], we will be able to fine tune the predictive tools to incorporate the patient's tumour and genomic characteristics that will help identify the subsets of patients with the greatest potential gains from regional therapies.

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## **ABBREVIATIONS:**

AN	Axillary node
GEP	Genetic expression profiling
IM	Internal mammary
IMN	Internal mammary node
PT	Peri-tumoural
SA	Sub-areolar
SLNB	Sentinel lymph node biopsy
SEER	Surveillance, Epidemiology and End-Results