Injection Techniques For Breast Lymphoscintigraphy: A Review

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Abstract

This review is a retrospective Meta analysis of 3133 patients evaluating injection techniques for breast lymphoscintigraphy in patients with early stage breast cancer. The optimal protocol for breast lymphoscintigraphy in early breast cancer patients was shown to employ areolar injection methods of radiocolloid over both blue dye and combined radiocolloid/blue dye techniques.

INTRODUCTION

Breast cancer is the most common cancer affecting females in Australia with a one in eleven life time risk for the average female ([1]). A one in 55 chance of mortality for sufferers makes breast cancer the second leading cause of female death ([1]).

The majority of breast carcinomas are seen to be defined as invasive ductal carcinomas accounting for approximately 70% of invasive breast cancer. This form of cancer is seen to possess a relatively low rate of local recurrence, however, it is associated with an overall worse prognosis than other common forms of breast carcinoma such as tubular (10%) and lobular (2-15%) carcinomas ([2]).

Nodal status is the most important determinant of survival in ductal carcinomas with a decrease in five year survival from 100% to 77% in patients with node positive examinations ([3]). The steadily increased incidence of breast cancer in the last thirty years in the majority of western countries is linked to an improvement in the implementation of early detection modalities and public health campaigns which have served to raise the diseases profile rather than an actual elevation in occurrence ([4]). For these patients early and accurate staging is crucial in order to determine treatment and ultimately surgical outcomes ([5]). The current method of staging is based on the TNM system and incorporates the assessment of primary tumour size and location (T), the regional lymph nodes (N) as well as the examination of distant metastases (M) ([3]).

Current non invasive imaging modalities are capable of accurately predicting parameter T as well as the presence and location of metastatic disease, however, the assessment of nodal involvement is more challenging ([6]). It is this parameter N which has the greatest bearing on the patients staging because axillary lymph node status is the greatest single clinical indicator of survival in patients with early breast cancer (table 1) ([7]). Accurate staging of this region is also crucially linked to the form of adjuvant therapy initiated within the patients treatment specifically chemotherapy regime and radiotherapy sites.

Figure 1

Table 1: Breast cancer survival by TNM stage ().

Stage	Five year survival
0	100%
I	100%
IIA	92%
IIB	81%
IIIA	67%
IIIB	54%
IV	20%

Clinical evaluation itself is not definitive because lymph node enlargement is not selectively related to metastatic involvement and a large percentage of those regional nodes

affected by tumour will not be palpable to physical examination ([3]). Thus, the only accurate method of assessing nodal involvement is seen to involve the histological sampling and examination of the tissues themselves. The current clinical gold standard for the evaluation of axillary lymph nodes for tumour cell migration is level one and two axillary lymph node dissection (ALND) in which between 10-30 lymph nodes are removed and sectioned for histopathology examination7.

Axillary lymph node dissection can result in significant morbidity including seroma, infection, pain, paresthesias and severe lymphoedema of the breast and upper limbs ([9]). Indeed clinical trials indicate that the rate of acute post surgical complications following ALND is as high as 20-30% with long term lymphedema appearing in 15-20% of patients ([7]). The greater number of nodes sampled with ALND, the higher the patients chance of severe postoperative morbidity. Thus, it is common practice to sample only a small portion of each node collected, leading to under sampling and an increased false negative rate ([3,10]).

LYMPHOSCINTIGRAPHY

The clinical application of breast lymphoscintigraphy has become widespread with departments worldwide employing this technique as an alternative to ALND in the evaluation of axillary node involvement. Currently, patients undergoing sentinel lymph node biopsy (SLNB) may also be referred for ALND where lymphoscintigraphy has failed to identify the correct lymphatic drainage pattern ([1]). Success of the technique varies widely and as such there is no universally accepted clinical protocol. Breast lymphoscintigraphy and SLNB aims to decrease morbidity and improve sensitivity in the detection of metastatic disease.

The sentinel lymph node can be defined as the first node in the regional lymphatic basin which receives lymph flow from a primary tumour ([11,12]). Clinically, the sentinel lymph node is used to predict the status of the entire regional lymphatic basin draining the tumour ([6]). Breast cancer cells invade newly formed lymphatic capillaries at the tumour surface; these capillaries enter larger lymphatic trunks and eventually reach the sentinel lymph node ([13]). When a sentinel node is free from tumour metastasis it is possible to exclude tumour spread to the regional lymphatic basin ([6]).

A ‘hot' sentinel node is defined as one where the ratio of counts/second in the sentinel lymph node is 10 times that of a non-SLN ([10]). Two criterions have been devised to define what is meant by the sentinel lymph node when using preoperative imaging. The first is simply the first node that appears to have high count statistics and the second is the visualisation of an afferent lymphatic vessel from the actual tumour site to a node ([14]).

A variety of radiopharmaceuticals are utilised for breast lymphoscintigraphy including, but not limited to; Tc-99m sulphur colloid, Tc-99m human serum albumin, Tc-99m nanocolloid and Tc-99m antimony sulphur colloid. Lymphatic drainage of radiocolloids (RC) when administered interstitially occurs over a period of hours with small particles being seen to flow first followed by intermediate particles. Larger sized colloid or albumin particles (>300nm) may become indefinitely retained at the injection site ([15]). Relatively small RC (< 50nm) allow rapid drainage and visualisation of the SLN, however, if surgery is delayed these agents have often progressed to second and third tier nodes leaving negligible activity within the true SLN ([16]). The SLN is visualised more consistently when 200-1000nm of sulphur colloid is utilised ([15]) although 100-200nm has also been reported as ideal ([17]).

BLUE DYE

The rationale behind the use of blue dye (BD) is based on the concept that both RC and BD will utilise the same lymphatic pathways to arrive at identical axillary nodes in a fashion similar to tumour metastases ([13]). BD is seen to provide a visual marker for the surgical team. When utilised in combination with RC guided SLNB, BD has been reported to increase the success rate for visualisation of SLNs, lowering the false negative rate and increasing the number of nodes harvested during surgery ([5]).

Administration of BD may introduce a number of side effects ranging in severity from staining of the skin and urine to anaphylaxis ([18]). Once administered, BD rapidly infiltrates the interstitial space resulting in a loss of contrast between the SLN and background regions ([5]). To overcome this, blue dye is commonly administered immediately prior to surgical excision of the SLN ([17]).

INJECTION METHODS

The importance of the correct injection method is highlighted by the observation that with a different site of injection a different SLN can be identified in 50% of patients ([19]). Thus, even employing methods with small variation in location and depth, dramatic differences in the observed drainage routes may be seen ([19]). Nieweg et al. identified

seven key methods of dose administration have been identified for breast lymphoscintigraphy ([19]):

- intratumoural (IT),
- intradermal (ID),
- subdermal (SD),
- periareolar (PA),
- subtumoural (ST),
- subareolar (SA),
- peritumoural (PT).

While all involve the direct injection of a radiolabelled colloid into the patient's breast tissue, their exact locations, number of injections, dose volume and dose activity vary significantly ([19]). IT and ST are not widely reported in the literature and, thus, do not feature in the following analysis while an eighth technique, intraparenchymal (IP), has widespread use.

METHODOLOGY

A retrospective review was performed on a total of 3313 patients with infiltrating breast carcinoma (T1 – TIIB, 0.4 – 3cm, N0 – N2, M0) in 35 peer reviewed manuscripts. These patients underwent sentinel lymph node mapping, using a combination of radiotracer and blue dye or either radiotracer or blue dye alone. In all cases identified SLN's once removed in surgery underwent histopathology using standard hematoxylin and eosin (H & E) with or without immunohistochemistry. All the patients were women, ranging in age from 21 – 90 years (mean 56.7 years). Preoperative diagnosis was obtained by physical examination, mammography and ultrasonography, followed by needle aspiration cytology or excisional biopsy.

Radiotracer injection was performed either the day before or the day of surgery. The time between injection and surgery using a one day protocol varied from 1-12 hrs. A large variety of radiotracers were used including: Tc-99m sulphur colloid, Tc-99m human albumin and Tc-99m albumin nanocolloid. Tc-99m sulphur colloid was the radiocolloid of choice in combination with a 0.22μm filter in 57% of the literature.

Where SD/ID administration of the radiotracer was performed (group 1), the dose varied from 3.7- 40 megabequerels (MBq) in 0.2- 0.5mL. Breast massage was performed in 37.5% of patients for 2-5 mins to facilitate radiotracer movement through draining lymphatics. Where IP/PT administration was performed (group 2), the dose varied from 7 – 185 MBq in 0.4 – 8mL. The radiotracer was injected in equal amounts in four quadrants surrounding the primary tumour or biopsy cavity. Breast massage was performed for 2-5 mins in 30% of the patients following the injection of the radiotracer. Where SA/PA administration of tracer was performed (group 3), the dose varied in activity from 18.5 – 40 MBq in 0.2 – 0.5mL. The radiotracer was injected in two injections to the tumour quadrant. Breast massage was performed in 33.3% of patients for 2-5 mins.

For all groups, lymphoscintigraphy was performed using a large field of view gamma camera with a high resolution collimator. Immediately after the radiotracer injection, continuous images were obtained until a draining lymph node was identified by radiotracer uptake. Once the sentinel node was visualised, static images were obtained from a variety of projections. In addition, a point source of Tc-99m, or alternatively a transmission source, was used to outline the contours of the patients shoulder and axilla. This served to provide better localisation of the identified nodes for surgical review, minimising the size of excision and surgical exploration required. All identified lymph nodes were then marked with indelible ink on the patient's skin.

Following general anaesthesia, 87.5% of patients in group 1 received 2 – 5mL of 1% isosulfan blue dye (Lymphazurin) given in 4 – 6 aliquots around the breast site. In group 2, 80% of patients had 1% isosulfan blue dye (Lymphazurin) administered in 2 – 5mL, given as 4 aliquots around the breast site. Similarly, 66.6% patients of group 3 received 2 – 5mL of 1% isosulfan blue dye (Lymphazurin) administered in 1 – 2 aliquots around the breast site.

RESULTS

Patients in the three injection type sub-groups were similar in age, tumour size and location (T), extent of regional lymph nodes (N) and tumour histology. A successful blue dye sentinel node biopsy was defined as a lymph node with visible blue staining. Successful radiotracer localisation required the ratio of counts/sec in the sentinel node to be 10 times that of a non sentinel lymph node. The success rate of both RC and the combined RC/BD strategies demonstrated statistically significant superiority over BD alone ($P < 0.001$) (table 2). Despite an increase in the successful visualisation rate, the combined RC/BD strategy was not shown to be statistically superior to RC alone ($P > 0.05$). The SA/PA

injection technique was shown to be superior to both SD/ID and IP/PT for all 3 imaging strategies (all $P < 0.001$) (table 3). IP/PT was superior to SD/ID for BD and combined RC/BD ($P < 0.001$), however, no statistically significant difference was noted in the performance of SD/ID against IP/PT for RC alone ($P > 0.05$).

Figure 2

Table 2: Comparison between visualisation techniques.

	BD	RC	RC/DB
Patient Number	1277	1060	976
Visualisation	970/1277 (75.9%)	947/1060 (89.3%)	915/976 (93.8%)
Non Visualisation	307/1277 (24.0%)	112/1060 (10.6%)	60/976 (6.1%)

Figure 3

Table 3: Lymphatic mapping results.

	BD	RC	RC/DB
Subdermal/ Intradermal			
Visualisation	50/134 (37.3%)	186/ 213 (87.3%)	80/94 (85.1%)
No Visualisation	84/134 (62.6%)	27/213 (12.7%)	14/94 (14.9%)
Intraparenchymal/Peritumoural			
Visualisation	809/1023 (79.0%)	642/727 (88.4%)	717/ 762 (94.0%)
No Visualisation	214/1023 (20.9%)	84/727 (11.6%)	44/762 (5.8%)
Subareolar/Periareolar			
Visualisation	11/120 (92.5%)	119/120 (99.2%)	118/120 (98.3%)
No Visualisation	9/120 (7.5%)	1/120 (0.8%)	2/120 (1.6%)

DISCUSSION

In the 2005 analysis of SLNB by the Australian government, patients with non localisation of the SLN were routinely referred on for axillary clearance ([1]). As a result, the cost of patients in whom the SLN is not visualised is significantly higher, between $10,876 and $112,732 per patient. These patients also experienced relatively higher levels of morbidity and mortality with an individual patient having a 0.32% chance of death following ALND and SLNB versus 0.08% for SLNB alone.

The SA/PA injection method offers many advantages compared to the IP/PT or SD/ID methods including simplified technique, rapid identification of SLN's and reproducible injection placements ([1]). The superiority of the SA/PA injection technique highlighted in this analysis is concordant with similar findings by the Veterans Affairs Medical Centre in Atlanta ([20]). Clinically, this method may be overlooked due to increased patient discomfort and its inability to differentiate extra axillary nodes. The pain experienced by the patient may be compensated for by a topical anaesthetic. Another potential downfall of the SA/PA method is the inability to visualise intra mammary chain (IMC) drainage. Those patients with extra axilla metastatic involvement possess a higher level of mortality at five years post staging than those in whom regional lymphatics contained no migratory flow. Despite this, it is not routine practice to assess the IMC nodes for involvement during lymphoscintigraphy.

RC alone provided superior rates of true positive SLN visualisation combined with the lowest level of false negative rates (99.2% and 0.8% respectively) using the SA/PA injection technique. The efficacy of combining RC and BD is overall superior to either RC or BD alone, however, RC/BD has lower visualisation rates for the SA/PA injection method; although not statistically significant. This is most likely to be due to a failure of the BD to be accurately absorbed into the lymphatics through the areolar plexus resulting in poorer lymphatic drainage visualisation; a theory which is supported by the 7.5% false negative rate of BD alone. The areolar injection methods, compared to the two other injection techniques, has consistently better results across the BD, RC and combined protocols in terms of SLN localisation.

The optimal protocol for breast lymphoscintigraphy in early breast cancer patients is the use of RC alone, administered through the SA/PA method.

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