Sentinel lymph node biopsy, axillary dissection and breast cancer: Radiation oncologist's viewpoint

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ABSTRACT

Sentinel lymph node (SLN) identification and biopsy in breast cancer have been carried out successfully since the early 1990s. In early-stage breast cancer, the negative predictive value of a SLN biopsy is as high as 93%–100%. With a negative SLN, no axillary treatment would be required and the breast can be treated by tangential radiation fields. Currently, for a patient with a positive SLN, axillary dissection is recommended. Axillary irradiation can replace surgery with a low risk of recurrence (< 7%). The modern practice of radiotherapy, delivering a dose of 50 Gy to the axilla, has a low rate of late morbidity. Hence, it is now time to plan clinical trials comparing axillary irradiation with axillary dissection in SLN-positive, early-stage breast cancer. These approaches to the axilla, guided by the status of the SLN can reduce arm problems in women with breast cancer and improve their quality of life. Just as the treatment of the primary breast tumour has changed from Halstedian mastectomy to conservation surgery combined with breast irradiation, SLN biopsy may allow a move away from surgical axillary clearance and the associated morbidity in the future.

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INTRODUCTION

The histological status of the axillary lymph nodes is the most important prognostic factor in breast cancer patients, determining their adjuvant treatment and the survival outcome. About 80% of women undergoing axillary dissection have at least one postoperative complication in the arm such as lymphoedema, weakness, infection or restriction of shoulder movement along with psychological distress.[1] The addition of postoperative radiotherapy following axillary lymph node dissection (AND) increases the problems.[2] Hence, the role of AND mainly in early-stage breast cancer is being re-evaluated.

Patients who are not at risk of developing an axillary recurrence (i.e. node-negative, early-stage breast cancer) need to be identified. Clinical examination of the axilla, ultrasound, CT scan and MRI have been inconsistent tools. Since the 1990s, a potential alternative to AND is resection of the sentinel lymph node (SLN). Surgery for the primary tumour has moved away during the past two decades from Halstedian mastectomy to breast conservation therapy. More and more women now accept limited breast surgery combined with breast irradiation. During the past decade, systemic chemotherapy has become the standard adjuvant treatment, based upon the size of the primary tumour. If the status of the axillary nodes can be determined by SLN biopsy, then surgery of the axilla can be avoided.[1]

The concept of SLN was first introduced in cancer of the penis and subsequently in malignant melanoma.[1,3] Cabanas termed the SLN as the node which first receives lymphatic drainage from the site of the tumour; subsequent spread occurs only when this lymph node is involved.[3] Thus, there is an orderly progression of tumour cells within the lymphatic system. In breast cancer, the SLN is usually detected close to the tail of the breast in the axilla. In a majority of patients, only a single node is identified but more than one node may be detected.

Radiation therapy (RT) is an important adjuvant modality in the management of breast cancer, as it is effective in decreasing locoregional recurrence and improving the overall survival.[4] In early-stage breast cancer patients, whether treated by breast conservation or mastectomy, current surgical practice includes AND (at least of levels I and II axillary lymph nodes). The addition of RT to the axilla depends on the histopathological status of the biopsied nodes. During the past few years, evidence (level II evidence and grade B recommendation; see Box)[5] from well-designed, multicentric studies and controlled case series has shown the feasibility of the technique of SLN biopsy and its high accuracy and predictive value. In fact, several institutions in the USA, Europe and the UK have started using SLN biopsy to make definitive decisions regarding AND.[6,7] Such alterations in the surgical approach to the axilla are likely to be matched by changes in RT policies, since axillary irradiation following AND is known to cause long term

EVIDENCE-BASED MEDICINE

Levels of evidence	*Grades of recommendation*
I From meta-analysis of randomized or at least one randomized controlled trial.	A Requires at least one randomized controlled trial in the literature (Evidence level I)
II From at least one well-designed study without randomization or one other well-designed quasi-experimental study	B Requires well-conducted clinical studies but no randomized clinical trials on the topic as part of the body of literature (Evidence level II–III)
III From well-designed, non-experimental, descriptive studies, such as comparative studies, correlation studies and case series	
IV From expert committee reports or opinions and/or clinical experience of respected authorities	C Indicates absence of directly applicable clinical studies of good quality (Evidence level IV)

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morbidity. There is a need to evolve future RT strategies in a controlled manner, both for SLN-negative and -positive patients.[8]

This article reviews the techniques of SLN mapping and biopsy, the findings from SNL biopsy studies, and their influence on the future role of RT in the management of the axilla in patients with early-stage breast cancer.

TECHNIQUES OF SLN BIOPSY

The SLN in the breast is identified intraoperatively in two steps.

Step 1

The SLN is identified either by lymphatic mapping or by lymphoscintigraphy. Lymphatic mapping is done by intradermal or peritumoral injection of vital blue dyes, most commonly isosulphan blue 1% and patent blue-V 2.5%. These dyes are selectively taken up by the lymphatics with minimal diffusion into the soft tissues.[9,10] The dye is picked up by the SLN in 5–30 minutes. A repeat injection may be necessary after 20 minutes. The use of vital blue dyes has some drawbacks. Visualization or dissection of the blue-stained lymphatic vessels and nodes in the lymphatic basin may be difficult. Also, the dye may pass rapidly to non-SLNs and then pose difficulty in identifying the true SLN.[11]

Lymphoscintigraphy was introduced for more accurate identification and verification of the SLN.[12] In this procedure, 0.4–1 mCi of radionuclide (technetium^{99m}-labelled antimony sulphide colloid) is injected around and into the tumour. The SLN is picked up as a hot spot on a hand-held gamma probe intraoperatively (at 120–240 minutes). However, the optimal technique of lymphatic mapping utilizes a combination of vital blue dye and radiolabelled colloid.[13]

Step 2

The identified SLN is then biopsied by placing an incision in the infraclavicular fossa just outside the axilla. Histological and immunohistochemistry examinations are done to establish whether the node is 'negative' or 'positive' for metastasis. It is ideal to carry out serial sectioning of the biopsied SLN(s) to increase the diagnostic yield.[11] Till date, SLN identification and biopsy is followed by AND to assess the predictive accuracy of the SLN technique.

REVIEW OF STUDIES ON SLN BIOPSY IN BREAST CANCER

Initial studies using either blue dye[14] or radiolabelled lymphoscintigraphy[12,15] were published in the early 1990s. In 1994, Giuliano *et al.* first reported the results of SLN biopsy in 174 breast cancer patients using only the blue dye technique.[14] The axillary status could be predicted in 96% of cases, out of which 36% were positive for metastasis. The false-negative rate of SLN biopsy was 12%. Other studies have shown false-negative rates ranging between 0% and 17%.[15,16] In 1997, Veronesi *et al.* using lymphoscintigraphy and gamma probe for detecting SLN, showed a false-negative rate of 5%.[17] Recently, various studies have shown that results with the combined use of blue dye and scintigraphy are better than with either of the techniques alone, with a false-negative rate of 0%–5% in most series.[11,13] The results of various studies[1,13,14,16–21] and the technique used in each are shown in Table I.

For evaluating the accuracy of SLN biopsy, the negative predictive value (NPV) is the most important (the probability of the patient being axillary node-negative when the SLN on biopsy is tumour-negative). The NPV ranges between 93% and 100% in most studies.[1,11,13,17,21] SLN identification is successful in 95% of cases after an initial learning curve. Correct prediction of the axillary status is feasible in 95% or more cases, the false-negative rate is less than 10% and the SLN on biopsy is positive for metastasis in 30%–40% of cases. These consistent findings from several studies (Table I) provide both qualitative and quantitative information[1,6–8] establishing the credibility of the practice of SLN biopsy.[5,7,13,20]

TABLE I. Results of studies of sentinel lymph node biopsy in breast cancer

Author (year)	Technique	*n*	False-negative rate (%)	Prediction of axillary status (%)	Node-positive patients (%)
Giuliano (1994)[14]	Blue dye (isosulphan)	174	12	96	36
Folscher (1997)[18]	Blue dye (methylene blue)	79	12	85	51
Flett (1998)[16]	Blue dye (patent blue-V)	68	17	95	31
Veronesi (1997)[17]	Scintigraphy	163	5	98	53
Borgstein (1998)[19]	Scintigraphy	130	2	98	42
Krag (1998)[1]	Scintigraphy	443	11	97	25
Albertini (1996)[20]	Scintigraphy and blue dye	62	0	100	32
Cox (1998)[13]	Scintigraphy and blue dye	466	1	100	23
Reynolds (1999)[21]	Scintigraphy and blue dye	222	–	97	27

Advantages

The technique of SLN biopsy is associated with certain advantages and disadvantages. A detailed analysis of one or two SLN in operable breast cancer offers an accurate and cheap method of staging the axilla in more than 90% of patients and the procedure has limited morbidity. As only one-third of patients with early breast cancer have nodal metastases, routine AND exposes a substantial number of patients to an increased operative morbidity without any known therapeutic benefit. Giuliano (the pioneer in SLN) has recently questioned the utility of either AND or limited axillary sampling, since SLN biopsy is a more directed, anatomical approach to the axilla.[7] In view of the good NPV, adjuvant therapy—surgery/radiotherapy or both—can be determined for those patients who definitely need it.

Disadvantages

The technique of SLN evaluation has certain drawbacks. There is a learning curve but the technique has undergone refinements in recent years.[1,6,7,10,13] In the presence of a positive SLN, 38%–67% of patients harbour non-sentinel metastatic nodes in the axilla. Skip metastasis to levels in axillary nodes higher than the SLN is possible and the incidence is 1%–12%.[1,11] Second, frozen section histological evaluation of the SLN has a false-negative rate of ≥10%.[22] Serial sectioning, immunohistochemistry and polymerase chain reaction (PCR) are the assessments done towards obtaining a more accurate histological status of the SLN biopsy.[1,6,11,13] Third, internal mammary nodes can be the first site of lymphatic involvement in about 20% of patients, mostly those with inner quadrant lesions.[13]

Ideally, the SLN technique to predict axillary status is not advisable for a primary tumour larger than 2 cm, tumours located in the axillary tail and in oestrogen receptor-negative women.[21] In

recent years, certain institutions from the UK (namely Nottingham and Edinburgh) have used limited axillary approaches such as axillary sampling or level I node dissection, with the argument that it is technically less cumbersome and has a higher predictive value compared to SLN biopsy.[23] However, locating micrometastasis intraoperatively is not easy; frozen section analysis here has the same fallacy as SLN biopsy, and random axillary sampling has a false-negative rate of 4%–40%.[7,24] Thus, SLN is considered to be a better reflection of the tumour status of the entire axillary node basin. The repeated validation of SLN biopsy has prompted workers to consider this as a method of choice for axillary staging in early breast cancer.[7,25] In spite of a learning curve and the cost related to lymphatic mapping, SLN biopsy may indeed prove to be a major advance in the surgical treatment of breast cancer, and clinical trials based upon SLN biopsy are encouraged.[26]

Randomized trials are being conducted by the National Surgical Adjuvant Breast Project (NSABP–B32), American College of Surgeons (ACOSOG–Z0011), Medical Research Council, UK (ALMANAC), European School of Oncology, Dutch and Danish groups.[6,21–24,26] These trials broadly consist of two groups: (i) those in 'negative' SLN patients in whom completion AND and observation are being compared, and (ii) those in 'positive' SLN patients where completion AND is being compared with observation or axillary RT.[6,7,21,22,25]

INFLUENCE OF SLN BIOPSY ON RADIATION THERAPY POLICIES

For the past five decades, AND in breast cancer has been the best available method for staging the axilla and selecting the appropriate adjuvant therapy.[7] If AND is avoided, the quality of life of breast cancer patients would improve.[2,6] The addition of postoperative irradiation increases the complication rate of axillary surgery.[8,24,27,28] After the introduction of the concept of SLN, it is possible that RT policies for the axilla may require to be altered.[6,8,21–24] Of course, much depends on the histopathological status of the SLN. Patients with negative SLN have an axillary failure rate of <10% if no further adjuvant therapy is given.[7,22,24] Hence these patients, provided the disease is in stages I or II, may not require mandatory AND and could be treated with breast irradiation alone. The currently used tangential breast irradiation technique following breast conservation surgery ordinarily includes the lower portion of the axilla (level I and part of level II, where the non-SLN may harbour metastasis in an SLN-negative patient) in the same photon fields.[22,24,26] This approach has found favour since the risk of nodal failure following tangential breast irradiation is as low as 1% (compared to the earlier high of 10%).[24]

The risk of axillary failure after a positive SLN is 33%–66% if no further treatment is advocated.[8,22,24] Controversy still exists about the usefulness of AND in such patients as it leads to long term arm problems and psychological distress in more than 80% of patients.[2,18,21,25] Two-thirds of these early breast cancer patients will not have nodal metastases and derive no therapeutic benefit from AND, and the rest who harbour metastases will still need adjuvant axillary irradiation.[4,22–26] An alternative to axillary dissection is axillary irradiation after a positive SLN and there is a need to evaluate whether this is equally efficacious. Although there are no randomized studies comparing completion AND with axillary irradiation in patients with a positive SLN, several studies have compared limited axillary sampling and axillary irradiation with AND. It was observed that axillary failure occurred in 3%–7% of patients with either AND or irradiation and the functions of the shoulder and arm are better in irradiated patients, when a full AND is not done.[22,24] Some concern was raised by a Nottingham trial which had an axillary failure rate of 11% in irradiated patients following positive axillary sampling. However, this was much lower than the 41% recurrence seen in non-irradiated patients and details of the RT technique were not described. In contrast, another trial from the UK (Edinburgh) showed that axillary RT following positive axillary sampling or a complete AND had similar failure rates (3%).[24]

From the point of view of management, the technique of axillary irradiation has improved substantially in recent years.[8,22,24,28] Radiation is currently given by a single anterior photon field directed to the full axilla and supraclavicular fossa at a depth of 5 cm to a total dose of 45–50 Gy in conventional fractionation. A posterior booster dose of 6–10 Gy can be given as and when required.[8,22,24] The evidence from SLN biopsy studies during the past decade make a case that both axillary dissection and axillary irradiation can be equally effective in patients with a positive SLN as far as locoregional control is concerned. Yet a major concern for these cured, early breast cancer patients is the long term treatment-related morbidity.[1,2,8,28] Although earlier reports favour AND as the treatment of choice, with better understanding of the pathophysiology of radiation-induced damage and the modification of radiation techniques, the risk of late complications due to radiation can be reduced to acceptable limits.[8] In a Danish Breast Cancer group trial, patients were randomized to postmastectomy RT and systemic treatment versus systemic treatment alone.[27] The incidence of late morbidity was higher in irradiated than in non-irradiated patients (Table II). However, the techniques of radiation have been critically evaluated and it has been seen that the role of AND in the development of lymphoedema, numbness and shoulder problems cannot be underestimated.[8,28] Patients who undergo complete axillary dissection (levels I, II and III) are most likely to develop complications even without the addition of postoperative irradiation.[7,26] The addition of RT to AND increases the morbidity. Hence, by avoiding AND in SLN-positive patients and by taking advantage of current axillary RT techniques, one can safely control the nodal recurrence as well as reduce treatment-related arm problems.[24]

The late effects of RT are not only related to the total dose of RT to the axilla (mentioned earlier) but also to the dose per fraction, which should be 1.8–2 Gy.[8] Besides the treatment-related factors involved in the development of arm problems, there are certain patient-related factors which affect the severity of late morbidity. These include old age, obesity, hypertension and subcutaneous fibrosis.[8] Thus, RT can be delivered with a decrease in the severe late morbidity if certain predisposing factors are taken into consideration (Table III). The management of early breast cancer may shift towards replacement of AND by axillary irradiation in future. Although this appears a simplistic statement, it is time to plan such clinical trials. These trials will answer many of the questions surrounding SLN biopsy, while protecting patient interests through the informed consent process.[26] In fact, ALMANAC (UK) and the European School of Oncology studies are already comparing complete AND with axillary RT in SLN-positive patients.[6]

TABLE II. Incidence of morbidity after axillary node dissection: Irradiated versus non-irradiated patients[27]

Morbidity	Irradiated (%)	Non-irradiated (%)
Lymphoedema	14	3
Mild shoulder impairment	45	15
Symptomatic shoulder impairment	17	2
Moderate-to-severe shoulder impairment	5	0

TABLE III. Predisposing factors for radiation-induced arm problems[8]

Treatment-related
Extent of axillary surgery
Use of concomitant chemotherapy
Radiation-related
Use of orthovoltage or supervoltage machines
Unequal weighted anterior/posterior fields
Larger dose per fraction (>2 Gy)
Beam modifying devices not used
Re-irradiation
Patient-related
Old age
Obesity
Hypertension
Shoulder exercises not practised
Collagen vascular diseases

CONCLUSION

Every new therapeutic intervention opens up new vistas and SLN in breast cancer is bringing into focus several treatment strategies which can be tried and tested. The change from Halstedian mastectomy to conservation surgery combined with breast irradiation has benefited thousands of women. AND has more to do with staging the axillary nodes than offering any therapeutic benefit and its attendant long term morbidity is substantial. Management of the axilla thus needs a careful reappraisal in terms of treatment-related quality of life and survival.[2,7,8,24,25,28] SLN biopsy has been proven to play an important role in staging of the axilla in breast cancer. This provides an opportunity to avoid extensive axillary dissection and also to choose appropriate adjuvant treatment. Patients with early breast cancer have a good prognosis and, therefore, should receive the best treatment so as to improve survival and quality of life, and decrease long term morbidity. In this context, axillary irradiation can offer cure along with reduction in axillary morbidity to <1% if modern RT techniques are used.[8,28]

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