**SURGICAL MANAGEMENT OF THE AXILLA IN EARLY BREAST CANCER**

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**Biosketch for Dr. Ismail Jatoi**

Dr. Ismail Jatoi is Professor and Chief of the Division of Surgical Oncology and Endocrine Surgery at the University of Texas Health Sciences Center in San Antonio, Texas. He is the holder of the Dale H. Dorn Endowed Chair in Surgery. Dr. Jatoi obtained his undergraduate bachelor’s degree from Washington University in St. Louis and his MD and PhD degrees from St. Louis University. He is a diplomate of the American Board of Surgery and a fellow of the American College of Surgeons. He completed fellowship training in surgical oncology at the Royal Marsden Hospital in London, England. Dr. Jatoi served in the U.S. military for many years, and was a Professor of Surgery at the Uniformed Services University in Bethesda, Maryland. He has received numerous military awards, including the Bronze Star and Legion of Merit, and retired from the U.S. Army with the rank of Colonel. Dr. Jatoi has had a longstanding interest in the treatment of breast cancer, the management of women at increased risk for breast cancer, and cancer epidemiology. He has a particular interest in the design and analysis of cancer clinical trials. Dr. Jatoi has previously served on the Breast Cancer Executive Committee of the Southwest Oncology Group (SWOG). Additionally, he is the Principal Investigator of the NRG Oncology Group at the University of Texas Health Science Center, and serves on the national NRG Oncology Breast Cancer Committee and Working Group.

**Biosketch for Dr. John R. Benson**

Dr. John Benson is a Consultant Breast Surgeon at Addenbrooke’s Hospital, Cambridge, UK. He qualified from Oxford University Clinical School and was awarded doctorates from Oxford and Cambridge Universities (DM (Oxon); MD (Cantab)). He received specialist training at the Royal Marsden Hospital and Institute of Cancer Research, London and The New York Hospital-Cornell Medical Centre, New York. Professor Benson is a Fellow and Director of Clinical Studies at Selwyn College, Cambridge and Visiting Professor at the School of Medicine, Anglia Ruskin University, Cambridge, UK. He is an examiner for the MRCS examination, a member of the British Breast Group and the Executive Board of the Association of Breast Surgery (Ordinary Trustee). His clinical practice is devoted entirely to breast diseases and current research interests include investigation of a fluorescent navigation system for sentinel lymph node detection. Dr Benson has more than 120 published articles in leading journals including The Lancet, Lancet Oncology and The British Journal of Surgery and has written numerous book chapters and several books in the field of breast diseases (winner of First Prize in the Oncology Section of BMA Medical Book Awards (2013). He is a former member of the Planning Committee for the San Antonio Breast Cancer Symposium (2013 – 2015).

**IN BRIEF**

From antiquity until the late 19th century, the management of breast cancer was largely predicated upon the humoral theory, which Galen (129-210 AD) espoused. Breast cancer was attributed to an excess of “black bile”, and the tumor itself regarded as a coagulum of black bile. Although Galen viewed breast cancer as a systemic disease, he nonetheless advocated surgery for the treatment of its local manifestations. In 1866, Rudolph Virchow undertook autopsy studies and observed that women who died of metastatic breast cancer generally harbored metastasis in the axillary nodes. Based upon these observations, Virchow proposed that breast cancer spread in an orderly fashion from the breast to the axillary lymph nodes and then to distant sites. In keeping with Virchow’s hypothesis, William Halsted proposed the radical mastectomy for the treatment of primary breast cancer, wherein the breast, pectoralis muscles, and ipsilateral axillary nodes were extirpated en bloc. Thus, in the late 19th century, breast cancer surgery was closely intertwined with axillary lymph node surgery.

Within a few years after widespread implementation of the Halsted radical mastectomy, it became evident that approximately 30% of women who were node-negative at the time of surgery ultimately succumbed from metastatic breast cancer. This observation was inconsistent with the Virchow-Halsted hypothesis, and alluded to the existence of alternate pathways for distant spread of the disease. In the 1970s, two large randomized trials (the Kings/Cambridge trial in the UK and the National Surgical Adjuvant Breast and Bowel Project (NSABP)-04 trial in the USA were launched to test the tenets of the Virchow-Halsted hypothesis. These trials randomized patients with a clinically node-negative axilla to either early or delayed treatment of the axilla (with either surgery or radiotherapy). The delayed treatment of the axilla did not adversely affect outcome, suggesting that axillary lymph node metastases was not the primary source for distant spread of breast cancer, and alternate means of dissemination (perhaps hematogenous) were responsible for poor outcomes.

Yet, despite the results of the Kings/Cambridge and NSABP-04 trials, complete axillary lymph node dissection (ALND) remained an integral component of the surgical treatment of early breast cancer until the late 20th century. There were two reasons for the enduring relevance of ALND. First, in patients with clinically node-negative breast cancer, failure to treat the axilla with either surgery or radiotherapy could substantially increase the risk of axillary recurrence, some cases of which were uncontrolled and severely impaired quality of life. Secondly, adjuvant systemic therapy was widely implemented for the treatment of breast cancer in the 1980s, and the absolute benefit of adjuvant systemic therapy was greater for patients with node-positive than node-negative breast cancer. Thus, until the late 20th century, nodal status was vital for the adjuvant systemic therapy decision-making process. However, in more recent years, decisions concerning administration of adjuvant systemic therapy have been increasingly predicated upon tumor biomarkers (i.e., estrogen receptor (ER), progesterone receptor (PR), and HER-2 neu status).

Since the mid-1990s, there has been a de-escalation in the use of axillary surgery. Two randomized trials examined the effect of omitting axillary surgery altogether in elderly breast cancer patients, the International Breast Cancer Study Group (IBCSG) Trial 10-93 and an Italian trial. Both trials showed that breast cancer survival and overall mortality did not differ between the “axillary surgery” and “no axillary surgery” groups in elderly patients, with better quality of life in the “no axillary surgery” group. Also in the late 1990s, the sentinel lymph node biopsy (SLNB) concept was introduced, whereby the first lymph nodes in the axillary basin to receive drainage from the breast (i.e. the sentinel lymph nodes) were identified with either radiotracer, blue dye, or use of both agents. If the sentinel nodes harbor malignancy, then additional nodes in the axillary basin may as well, and complete axillary dissection is undertaken. On the other hand, if there is no evidence of metastasis in the sentinel nodes, then further axillary surgery is avoided. At least seven trials randomized clinically node-negative breast cancer patients to either the SLNB policy versus standard ALND. These trials consistently showed that morbidity is lower and quality of life better in patients who undergo SLNB compared to standard ALND, with no adverse effects on survival.

More recently, four trials, the American College of Surgeons Oncology Group (ACOSOG) Z0011, After Mapping of the Axilla: Radiotherapy or Surgery (AMAROS), International Breast Cancer Study Group (IBCSG) 23-01, and AATRM (Spanish), have randomized sentinel node-positive patients to either no further local therapy of the axilla versus completion ALND or radiotherapy to the axilla. Each of these was a non-inferiority trial, and found that avoidance of further axillary surgery in sentinel node-positive patients was not worse than completion ALND or axillary radiotherapy. These trials seem to suggest that a residual low burden of axillary disease can be safely treated with adjuvant systemic therapy and/or radiotherapy.

Neo-adjuvant systemic therapy may result in substantial downstaging of breast cancer. Until recently, there was reluctance to avoid complete ALND in patients following administration of neo-adjuvant systemic therapy, but there is now evidence that SLNB policy can be applied to these patients as well. For node-positive patients who convert to node-negative status, careful identification and evaluation of the sentinel nodes may potentially obviate the need for completion ALND and thereby reduce the morbidity of axillary surgery.

Finally, there are now trials underway to examine the possibility of avoiding axillary surgery altogether (also avoiding SLNB) in clinically node-negative patients with favorable tumor characteristics. These patients generally have either no disease in the axillary nodes or a low burden of disease that can be safely treated with adjuvant systemic therapy and/or radiotherapy. In these patients, biomarkers are utilized to determine eligibility for adjuvant systemic therapy. Thus, the surgical management of the axilla continues to evolve, with the aim of improving both local control of the axilla and quality of life.

**HISTORICAL BACKGROUND**

From antiquity until the late 19th century, the management of breast cancer was largely predicated upon the “humoral theory” proposed by Galen (129-210 AD) 1. Galen had suggested that breast cancer was a systemic disease, and he promulgated the humoral theory to account for its pathogenesis 2. Breast cancer was attributed to an excess of “black bile”, and the tumor itself regarded as a coagulum of black bile. However, Galen strongly advocated surgery for the treatment of breast cancer, and urged surgeons to “excise a pathologic tumor in a circle in the region where it borders on the healing tissue”3. Although surgical extirpation of breast cancer was common during this era, many of Galen’s disciples would often resort to nonsurgical treatments, such as special diets, purgation, venesection, and leaching. These alternatives to surgery were believed to be effective in getting rid of excess bile, and were often considered acceptable options for breast cancer treatment.

In 1757, the French surgeon LeDran challenged Galen’s humoral hypothesis, and proposed that breast cancer was a localized disease process that spread via the lymphatics to distant sites4. LeDran was one of the first surgeons to suggest that lymph node dissections should become an integral part of the surgical treatment of breast cancer. However, Galen’s humoral theory was still very popular throughout Europe in the 18th century, and LeDran’s hypothesis and his proposed treatment strategy were not readily accepted.

It was not until the late 19th century that breast cancer surgery became closely intertwined with axillary lymph node surgery. In 1866, Rudolph Virchow, a German pathologist, published his textbook “Cellular Pathology”, in which he reported the results of his autopsy studies5. Virchow observed that women who died of metastatic breast cancer generally harbored metastasis in the axillary nodes at the time of death. He postulated that the axillary lymph nodes served as the nidus for the distant spread of the disease. Thus, Virchow proposed that cancer spread in an orderly fashion from the breast to the axillary lymph nodes and then to distant sites.

William Halsted, an American surgeon who studied in Europe prior to embarking on a distinguished academic career at the Johns Hopkins Hospital, was intrigued by Virchow’s autopsy studies and hypothesis. Halsted proposed a novel plan for breast cancer treatment that took into account the Virchow hypothesis6. Halsted argued that if the axillary lymph nodes were indeed the sole nidus for the distant spread of breast cancer, then extirpation of these nodes should be an integral part of any cancer operation. Thus, Halsted promulgated the radical mastectomy (i.e., Halsted radical mastectomy), wherein the breast, pectoralis muscles, and ipsilateral axillary nodes were extirpated en bloc6,7. Halsted refined the operative technique during his tenure as head of the surgery department at the Johns Hopkins Hospital, and many prominent surgeons of this era were taught this operation. The Halsted radical mastectomy was modified in the early years of the 20th century, whereby the pectoralis muscles were retained to reduce disfigurement (ie. modified radical mastectomy)8. Yet, the tenets of the so called Halstedian paradigm encompassed in the radical mastectomy and first described in the late 19th century, remained the cornerstone for the treatment of breast cancer until the mid-1980s9.

**SIGNIFICANCE OF AXILLARY LYMPH NODE METATASES**

There were three important corollaries to this paradigm. First, nodal metastasis was viewed as a time-dependent variable, attributable to delay in breast cancer diagnosis and treatment10. This created a sense of urgency, and timely extirpation of breast cancers was considered paramount for achieving good outcomes. Secondly, meticulous dissection of the axillary lymph nodes was also believed to be essential for ensuring optimal long term outcomes11. Inadequate axillary clearance could potentially leave behind lymph nodes harboring tumor foci which could eventually serve as a source for distant metastasis. Finally, resection of a node-negative cancer was considered curative7. Indeed, if metastasis to the lymph nodes was a prerequisite for distant spread of cancer, then resection of a cancer with no evidence of lymph node involvement implied that surgical treatment had occurred in a timely manner, thereby preventing any distant dissemination of disease.

According to the Halstedian paradigm axillary lymph nodal metastases are an indicator of tumor chronology, and the more favorable prognosis of node-negative cancers is attributed to timely resection, before any sequential and orderly metastatic process via the axillary lymphatics had occurred 10,11. Yet, there is now evidence to suggest that nodal metastases are also a marker of tumor biology, with node-positive tumors having an intrinsically more aggressive phenotype12. Several years ago, the senior author’s group undertook a multivariate analysis of survival data from the San Antonio Breast Tumor Bank12. To reduce the uncertainty associated with lead-time bias, nodal status at initial diagnosis was correlated with outcome after relapse. Survival experience after first relapse in almost 1700 primary breast cancer cases was analyzed using Cox proportional hazards regression. The interval from relapse to death was examined for categories of patients with 0 versus 1-3 versus 4 or more nodes. It was found that patients with four or more involved nodes at initial diagnosis had a significantly worse outcome after relapse than node-negative cases, irrespective of duration of the disease-free interval. This data therefore supported the concept that nodal metastasis was not only an indicator of diagnosis at a later stage in the natural history of breast cancer, but also a marker of a biologically aggressive phenotype.

Within a few years after widespread implementation of the Halsted radical mastectomy, it became evident that approximately 30% of women who were node-negative at the time of surgery ultimately succumbed from metastatic breast cancer13. This observation was inconsistent with the Virchow-Halsted hypothesis, and alluded to the existence of alternate pathways for distant spread of the disease14. Yet, many in the surgical community refused to abandon the notion that nodal tumor deposits were a potential conduit for development of distant metastasis. Many prominent surgeons argued that other nodal basins, such as the internal mammary nodes or the supraclavicular nodes, might serve as lymphatic routes for the development of metastatic breast cancer15,16. More expansive lymphadenectomy, including resection of the internal mammary and supraclavicular nodal chains, was therefore proposed to maximize the chance of achieving cure. Yet, there was considerable attendant morbidity with these extended surgical procedures and these expanded lymph node dissections were ultimately abandoned. Thus, lymph node surgery for management of breast cancer remains confined to dissection of the axillary lymph nodes.

**EXTENT OF AXILLARY LYMPH NODE DISSECTION**

The extent of axillary lymph dissection is defined in terms of anatomical location of nodes in relation to the pectoralis minor muscle (Figure 1) 17. Those lymph nodes lying lateral to the pectoralis minor are designated as level I, those directly posterior to the muscle are level II, whilst nodes medial to the medial border of pectoralis minor are level III18. To undertake resection of level III lymph nodes, division or resection of the pectoralis minor muscle was often required, but nowadays retraction of the muscle should suffice. Generally, dissection of the axilla continues superiorly to the axillary vein, laterally to the latissimus dorsi muscle, medially to the chest wall (serratus anterior muscle), inferiorly to the interdigitation of the latissimus dorsi and serratus anterior muscles, and posteriorly to the subscapularis muscle18. Two motor nerves, the long thoracic (innervating the serratus anterior muscle) and the thoracodorsal (innervating the latissiumus dorsi muscle) should be identified and preserved during an axillary lymph node dissection. Injury to the long thoracic nerve results in a “winged scapula” which is disfiguring, and injury to the thoracodorsal nerve may lead to atrophy of the latissimus dorsi muscle19,20.

Observational studies suggest that more extensive axillary lymph node dissection is associated with improved survival when compared to less extensive nodal resection. For instance, in patients with clinical stage I breast cancer, removal of 10 or more nodes was associated with a statistically significant improvement in disease-free survival when compared to removal of fewer nodes21. However, these results could be explained by the phenomenon of stage migration bias22. To better understand this bias, consider a patient with a 1.5 cm cancer and a metastatic lymph node at level III of the axilla. If a surgeon performs a level I and level II dissection, then this patient would be categorized as having stage I breast cancer (the patient would be classified as node-negative because the positive node at level III would not be harvested). On the other hand, if a surgeon undertakes an axillary lymph node dissection to include level III on this same patient, then the nodal metastasis at level III would now be uncovered and the same patient would be categorized as having a stage II breast cancer. Thus, when patients are compared stage for stage, it may appear that the surgeons who perform level III dissections have better outcomes compared to those who confine dissection to level II nodes. However, this is not necessarily due to any surgical consequence, but rather to upstaging (stage migration) of patients who might otherwise be classified as stage I (level I – II dissection) to stage II ( level I – III dissection).

Randomized trials are therefore necessary to reduce this risk of stage migration bias. A large randomized trial was undertaken in Japan between May 1991 and April 1993 involving women treated with mastectomy for breast cancer 23. In this trial, 1209 women with stage II breast cancer were randomly assigned to undergo either a level I – II or a level I – III axillary lymph node dissection. The 10-year cumulative survival rate was 86.6% for level I- II and 85.7% for level I-III axillary dissection (hazard ratio (HR) 1.02; p=0.931, log rank test). The 10-year disease-free survival rate was 73.3% and 77.8 % respectively (HR 0.94, p=0.666). Thus, overall and disease-free survival rates were similar in both groups but associated blood loss and duration of surgery were significantly less for a level II dissection. The authors concluded that that there was no benefit from a level III versus a level II dissection in patients with clinical stage II breast cancer.

**REPUDIATION OF THE VIRCHOW-HALSTED HYPOTHESIS**

For more than a century, the management of breast cancer was largely predicated on principles enunciated by Virchow and Halsted24. Axillary nodes were viewed as a nidus for the distant spread of breast cancer, and prompt extirpation of the tumorous breast and adjacent axillary nodes was mandatory for any surgical procedure with curative intent. In the 1970s, two large randomized trials were launched to test the basic tenets of this hypothesis25,26. Specifically, these trials randomized patients with a clinically node-negative axilla to either early or delayed treatment of the axilla. If the Virchow-Halsted hypothesis was correct, then delaying definitive treatment of the axilla should have resulted in worse overall survival due to opportunity for distant spread from tumor deposits developing within the axillary nodes after clinical presentation.

In the United Kingdom, the Kings/Cambridge trial was launched in 1970, and it randomized 2243 women with clinically node-negative breast cancer to mastectomy and axillary radiotherapy versus mastectomy and observation of the axilla (i.e, the watch policy)25. After 10 years of follow-up, there was a substantially greater rate of axillary recurrence in the “watch policy” group (20%) when compared to the axillary radiotherapy group (2%). Yet, there was no difference in overall survival, indicating that delayed treatment of the axilla had no effect on mortality, and that the axillary lymph nodes were not the sole nidus for the distant spread of breast cancer.

In the United States, the National Surgical Adjuvant Breast and Bowel Project (NSABP)-04 trial was launched in 1971, and randomized more than 1000 women with clinically node-negative breast cancer to one of 3 arms: mastectomy and axillary dissection, mastectomy and axillary radiotherapy, or mastectomy with delayed axillary dissection in the event that nodes became positive (i.e., axillary observation group)26. After 25 years of follow-up, there was no difference in overall survival between the three groups, although rates of axillary recurrence were significantly higher in the observation group (20%) when compared to patients undergoing either the axillary radiotherapy (2%) or axillary surgery (2%) (Figure 2). These results were similar to those of the Kings/Cambridge trial, but inconsistent with the Virchow/Halsted hypothesis of progressive centrifugal spread of breast cancer. Axillary lymph node metastases did not appear to be the primary source for distant spread of breast cancer, and alternate means of dissemination (perhaps hematogenous) were invoked to account for these observations27.

Despite results of the Kings/Cambridge and NSABP-04 trials, complete axillary lymph node dissection remained an integral component of the surgical treatment of early breast cancer until the late 20th century28. There were two reasons for the enduring relevance of axillary dissection. First, the Kings/Cambridge and NSABP-04 trials demonstrated that, in patients with clinically node-negative breast cancer, failure to treat the axilla with either surgery or radiotherapy could substantially increase the risk of axillary recurrence, some cases of which were uncontrolled and severely impaired quality of life. Secondly, adjuvant systemic therapy was widely implemented for the treatment of breast cancer in the 1980s, and the absolute benefit of adjuvant chemotherapy was greater for patients with node-positive than node-negative breast cancer29. Although both surgery and radiotherapy at the time individually reduced the risk of axillary recurrence from about 20% down to 2%, nodal status could only be determined from surgical resection of nodal tissue and at the time was essential for the decision-making process in terms of adjuvant systemic therapy30.

Consider, for example, a patient with a 2 cm node-negative breast cancer who has an estimated 10% risk of death over a 10-year period. Adjuvant chemotherapy has a 25% relative benefit and would reduce that risk from 10% to 7.5% (a 2.5% absolute benefit). For such a patient, the toxicity of chemotherapy would outweigh any small absolute benefit, and this form of adjuvant systemic therapy would therefore be contraindicated. By contrast, if this same patient were found to have a node-positive breast cancer, then the risk of death could be as high as 40%. Under these circumstances, adjuvant chemotherapy would reduce the risk of death from 40% to 30%, representing an absolute benefit of 10% for chemotherapy which would now outweigh its risk of toxicity. Thus, during this era of early adjuvant chemotherapy, nodal status was a key factor in determining eligibility for such treatment and axillary lymph node dissection therefore remained an integral part of the decision-making process in respect of need for adjuvant systemic therapy.

**MORBIDITY OF AXILLARY SURGERY**

Axillary surgery can be associated with considerable morbidity. Thus, typically within two years following axillary surgery, patients report a variety of symptoms. These include some degree of axillary pain (39%), numbness or paresthesias on the operated side (68%), some degree of restriction of arm mobility (21%) dissatisfaction with the appearance of their axillary scar (15%), and at least some degree of arm swelling (lymphedema) is detectable in up to 75% of patients31. Sentinel node biopsy (discussed later in this monograph), can substantially reduce these untoward effects, but does not completely eliminate them. The morbidity of axillary surgery and its adverse impact on quality of life has been a topic of much discussion, and the impetus for efforts to reduce the extent of axillary surgery (or avoid it altogether) without compromising patient safety.

**DE-ESCALATION OF AXILLARY SURGERY**

Since the mid-1990s, there has been a gradual de-escalation of axillary surgery and several factors have contributed to this trend (Figure 3) 32. Firstly, screening mammography was introduced in the early 1980s and led to a substantial increase in the proportion of women presenting with in-situ breast tumors and node-negative breast cancers33. It quickly became evident that axillary surgery was not required for surgical treatment of ductal carcinoma in situ (DCIS), and might be unnecessary for selected patients with small screen-detected invasive cancers34. Secondly, there have been improvements in adjuvant treatments including systemic therapy and radiotherapy, and these adjuvant treatments may potentially eradicate a low burden of axillary disease35,36. Thirdly, biomarkers (estrogen receptor, progesterone receptor, and HER-2 neu receptor status) have now assumed greater importance in determining eligibility for specific adjuvant systemic therapy regimens, with a corresponding decrease in the relevance of nodal status in the adjuvant systemic therapy decision-making process37. Finally, neo-adjuvant systemic therapy can result in substantial down-staging of loco-regional disease, and this has potential implications for reducing the extent of axillary surgery even amongst patients who initially present with larger tumors38.

*Omission of Axillary Surgery in the Elderly*

Two randomized trials have examined the effect of omitting any kind of axillary surgery in elderly breast cancer patients39,40. In many instances, elderly patients have significant co-morbidities and are not candidates for adjuvant chemotherapy, and therefore nodal status would not influence decision-making with regards to administration of adjuvant chemotherapy. Between 1993 and 2002, the International Breast Cancer Study Group (IBCSG) Trial 10-93 recruited 473 patients aged 60 years or older with clinically node-negative operable breast cancer, for whom adjuvant tamoxifen therapy was planned39. These patients were then randomized to primary breast surgery plus axillary clearance followed by tamoxifen for 5 years versus the same without axillary clearance. Both mastectomy or lumpectomy plus radiotherapy were acceptable local therapy options within this trial. The primary endpoint was quality of life and the median age at entry was 74 years. The quality of life was better for the “no axillary surgery” group during the initial years after breast surgery, but this difference tended to disappear after 6 to 12 months. Moreover, after a median follow-up of 6.6 years, the disease-free survival and overall survival between the “axillary surgery” and “no axillary surgery” groups were similar. The investigators concluded that avoiding axillary surgery for women aged 60 or older with clinically node-negative breast cancer receiving tamoxifen yields similar efficacy combined with better early quality of life.

A similar randomized trial to assess avoidance of axillary surgery in elderly patients was initiated in Italy in 199640. That trial recruited 238 patients aged 65-80 years with cT1CN0 breast cancer, and randomized those patients to breast conserving surgery (BCS) with axillary dissection versus BCS without axillary dissection. Patients received whole breast radiation as well as tamoxifen for 5 years and endpoints in this trial were breast cancer mortality, overall survival, and cumulative incidence of axillary disease in patients not receiving axillary dissection. After 15 years of follow-up, breast cancer mortality and overall survival did not differ between the “axillary surgery” versus the “no axillary surgery” groups. The investigators concluded that avoidance of axillary surgery is feasible for patients who meet the eligibility criteria for this trial (elderly clinically node-negative patients with small tumors). For such patients, axillary surgery is indicated only in those rare instances when overt axillary disease develops during follow-up.

*Impact of Screening Mammography*

Screening mammography was introduced in the United States in the early 1980s, and its utilization increased rapidly in the years that followed41. Contrary to what one might expect, screening mammography does not substantially reduce rates (number of cases per 100,000 women) of more advanced lesions such as node-positive or metastatic breast cancer42. Nonetheless, it does increase the proportion of node-negative breast cancers, partly because it detects many small node-negative tumors that might otherwise have not been detected in the absence of screening (i.e., screening results in over-diagnosis)43. Thus, following the introduction of screening mammography in the 1980s, there has been a stage shift with greater numbers of women presenting with node-negative breast cancers and undergoing unnecessary axillary dissection. This has drawn attention to the substantial morbidity of axillary surgery, and the potential for reducing unnecessary axillary lymph node dissections.

*Sentinel Lymph Node Biopsy*

Since the widespread utilization of mammography screening in the USA in the early 1980s, there has been a substantial decrease in the incidence of node-positive breast cancers. To avoid unnecessary axillary surgery and minimize the risk of morbidity associated with this procedure, the sentinel lymph node biopsy (SLNB) technology was developed44. A tracer agent is injected in the periareolar or peritumoral area and usually consists of a combination of blue dye and radioisotope (although either agent can be utilized alone)45. The tracer localizes to the first lymph node(s) in the axillary basin to receive drainage from the tumor. The SLNB concept is based upon the premise that if tumor cells are identified in the sentinel node(s), then additional lymph nodes in the axillary basin may contain deposits of metastatic tumor as well. On the other hand, if no tumor is identified in the sentinel node, then it is unlikely that other lymph nodes in the axillary basin will harbor metastatic deposits. Indeed, patients with SLNB-positive tumors are 14 times more likely to have involvement of additional nodes in the axillary basin when compared to patients with SLNB-negative tumors46. Thus, the SLNB technology allowed surgeons to reduce the extent of unnecessary axillary surgery. Removal of only the sentinel lymph nodes is associated with far less morbidity than complete ALND47. The introduction of SLNB technology allowed surgeons to retain the accuracy of surgical staging and yet confine complete ALND to those patients with SLNB-positive tumors.

For patients with clinically node-negative primary breast cancer, at least seven randomized trials have compared SLNB policy (complete ALND only in sentinel node-positive cases for calculation of false negative rates) versus standard ALND48-54. The SLNB is the preferred option for management of the axilla in clinically node-negative breast cancer patients. For patients that are clinically node-positive, a level I/level II axillary dissection is generally recommended55. However, there is no uniform consensus as to what constitutes a patient with a “clinically node-negative” axilla, but it is generally considered to mean any patient with no evidence of axillary disease on histology, clinical examination (palpation of the axilla), or imaging (with ultrasound, mammogram, and/or breast MRI). In the seven trials that have examined outcomes following SLNB policy versus standard ALND, the primary and secondary endpoints have varied, and include overall survival, disease-free survival, local recurrences, and quality of life. These trials have consistently shown that morbidity is lower and quality of life better in patients who undergo SLNB compared to standard ALND, with no adverse effects on survival from lesser axillary surgery.

The largest of these SLNB trials was NSABP-B32, which randomized 5611 women between the years 1999 and 2004 to either SLNB plus ALND (group 1) versus SLNB alone with ALND only if the sentinel nodes were positive (group 2)48. The primary endpoint for this trial was overall survival, the Log-rank comparison after 8 years for groups 1 and 2 yielding a hazard ratio of 1.20 (95% CI: 0.96-1.50, p=0.12) and 1.05 (95% CI: 0.90-1.22, p=0.54) for overall and disease-free survival respectively. There were 8 regional node recurrences in group 1 and 14 in group 2 (p=0.22). This trial therefore demonstrated that SLNB neither compromised survival nor increased risk of recurrence, with no statistically significant differences between patients treated with ALND versus SLNB policy with respect to overall survival, disease-free survival and regional control.

Similarly, the Milan trial randomized patients to SLNB plus ALND versus SLNB alone (ALND only if the sentinel nodes were positive), with a total of 566 patients recruited between the years 1998 and 199949. After a median follow-up of 95 months, there were a total of 49 breast cancer-related events (local recurrences, regional lymph node metastases, and distant metastases), of which 26 were in the standard treatment group and 23 in the SLNB group (p=0.52). This trial likewise demonstrated that SLNB had no detrimental effect on risk of recurrence. Moreover, the Milan trial included a quality of life component and examined the effect of SLNB on morbidity. Axillary pain, paresthesias, restriction of arm mobility, and arm swelling (lymphedema) were found to be substantially reduced in patients randomized to SLNB (with ALND reserved only for patients with SLNB-positive tumors).

The Axillary Lymphatic Mapping Against Nodal Axillary Clearance (ALMANAC) trial was conducted in the United Kingdom and randomized 1031 patients with invasive breast cancer to either SLNB policy versus ALND/node sampling50. In the SLNB arm of the trial, patients that were SLNB-positive went on to receive either ALNB or axillary radiotherapy, depending on the protocol at the treating institution. The primary endpoints of this trial were arm morbidity and quality of life (assessed by multiple measures), and the secondary endpoint was axillary recurrence at 5 years. The relative risks of arm lymphedema and sensory loss for the SLNB group versus the ALND group at 12 months was 0.37 (95% CI: 0.23 to 0.60) and 0.37 (95% CI: 0.27 to 0.50), respectively. Overall patient-recorded quality of life and arm functioning scores were higher in the SLNB group compared with the ALND and this reached statistical significance.

Similar one-year outcomes were assessed in the Sentinel Node Biopsy Versus Axillary Clearance (SNAC) randomized trial conducted in Australia51. In that trial, 1081 women were randomly allocated to SLNB policy versus routine ALND (SLNB followed immediately by axillary clearance). In the SLNB policy arm of the trial, patients underwent completion ALND only if the sentinel nodes was positive or not identified (SLNB failure); otherwise, these patients underwent SLNB alone. The primary endpoint of this trial was increase in arm volume from baseline to the mean value of measurements at 6 and 12 months. This trial demonstrated that the average increase in arm volume was much lower (2.8%) in the SLNB group compared with the ALND group (4.2%), p=0.002.

Between the years 1999 and 2003, 298 clinically node-negative breast cancer patients were randomly allocated to either ALND versus SLNB policy (SLNB followed by ALND only in the sentinel node was positive) in a trial led by Arnie Purushotham at Addenbrooke’s Hospital in Cambridge, England52. A detailed assessment of physical and psychological morbidity was performed during a 1-year period postoperatively. The authors reported a significant reduction in postoperative arm swelling, rate of seroma formation, numbness, and loss of sensitivity to light touch and pinprick among patients in the SLNB policy arm of the study.

The Italian Sentinella/GIVOM trial randomized 749 patients between the years 1999 to 2004 to SLNB followed by compulsory ALND (ALND arm) versus SLNB followed by ALND only if the sentinel node showed metastatic tumor53. This trial reported a 5-year disease-free survival of 89.9% in the ALND arm and 87.6% in the SLNB arm, but there were too few patients enrolled in the trial to draw any robust conclusions. The authors claimed that SLNB was effective and well tolerated, but conceded that the safety and efficacy of this technique needed to be assessed in larger trials and meta-analyses.

In another Italian trial conducted at the National Cancer Institute in Genoa, 248 patients were randomized to either ALND versus SLNB (followed by ALND if the sentinel node was positive), between the years 1998 and 200154. At a median follow-up of 5.5 years, there were no axillary recurrences in the SLNB arm, with overall survival and event-free survival not statistically different between the two arms. It was initially planned to enroll 2570 patients in this study, but enrollment was prematurely interrupted as patients became aware of media reports alluding to promising results of the SLNB technique. Patients therefore increasingly declined randomization in a study where routine ALND was one of the alternatives.

In aggregate, these seven trials validated SLNB as the preferred method for management of the axilla in clinically node-negative patients with early stage breast cancer. Notably, when compared to routine ALND, the SLNB resulted in a 60% relative reduction in the risk of arm lymphedema which is acknowledged as the major cause of morbidity from ALND. Moreover, these trials consistently demonstrated that SLNB does not adversely affect overall survival or the risk of local or distant recurrence. Thus, the SLNB policy was regarded as a major contribution towards improving quality of life for clinically node-negative patients with primary breast cancer, and precipitated a trend of de-escalation of axillary surgery for the majority of early stage breast cancer patients.

*Avoidance of Further Axillary Surgery in Patients with Sentinel Lymph Node-Positive Tumors*

Although the NSABP-04 and Kings/Cambridge trials showed that treatment of the axilla (with either surgery or radiotherapy) did not influence overall survival, they did reduce the risk of axillary recurrence (from approximately 20% down to 2%)25,26. Nonetheless, in the years immediately following publication of the NSABP-04 and Kings/Cambridge trials results, knowledge of nodal status was deemed essential for determining eligibility for adjuvant chemotherapy, and for this reason axillary surgery remained an integral component of breast cancer local therapy56.

Notwithstanding this assertion, radiotherapy and adjuvant systemic therapies have much improved over time, and the risk of axillary recurrence has declined substantially57. This has prompted the viewpoint that more extensive axillary surgery (i.e., beyond sentinel lymph node biopsy alone) may no longer be necessary in patients with clinically node-negative breast cancer, even in circumstances where the sentinel node harbored metastasis58. SLNB alone (in conjunction with primary tumor characteristics) might provide sufficient information to guide adjuvant chemotherapy decision-making, and a low burden of residual axillary disease could potentially be eradicated with adjuvant systemic therapy and/or radiotherapy. To assess this possibility, four trials were undertaken randomizing sentinel node-positive patients to either further axillary surgery versus no further axillary surgery. These were the American College of Surgeons Oncology Group (ACOSOG) Z0011, After Mapping of the Axilla: Radiotherapy or Surgery (AMAROS), International Breast Cancer Study Group (IBCSG) 23-01, and the AATRM (Spanish) trials59-62.

Each of these four trials was based on non-inferiority, the underlying premise of which differs from that of superiority trials63. In the latter, the null hypothesis states that the experimental treatment and standard treatment are equal, and rejection of the null hypothesis (i.e. a positive result) means that the experimental treatment is superior to the standard treatment. By contrast, in a non-inferiority trial, the null hypothesis states that the experimental treatment is worse than the standard treatment by a pre-specified margin (i.e., the margin of non-inferiority). A positive result in a non-inferiority trial would mean that the experimental treatment is not worse than the standard treatment (i.e., that the endpoint for the outcome of interest rests within the margin of non-inferiority). The statistical procedure to test for non-inferiority is a one-sided test and alpha level of significance. Each of the above four trials demonstrated that for clinically node-negative patients with metastasis to the sentinel node, SLNB alone was non-inferior to SLNB+ complete ALND. Thus, it would appear that a low burden of residual axillary disease can be adequately treated with modern adjuvant systemic therapy and/or radiotherapy (in a multimodality context). Complete ALND with surgical extirpation of non-sentinel nodes is not necessarily required in such instances.

The extent of tumor deposits in the sentinel nodes was an important consideration in the ACOSOG Z0011, AMAROS, IBCSG 23-01, and AATRM trials. Macrometastases are defined as tumor deposits within the sentinel node that exceed 2mm, micrometastases range between >0.2 and< 2 mm, and isolated tumor cell (ITC) are not larger than 0.2mm. The IBCSG-23-01 only included patients with tumor deposits in the sentinel nodes less than or equal to 2mm (isolated tumor cells and micrometastases, but not macrometastases), while AATRM included patients with micrometastases but excluded those with ITC or macrometastases. In contrast, the ACOSOG Z0011 and AMAROS trials included patients with both micro metastases and macrometastases.

The results of these trials have generated considerable controversy. The IBCSG 23-01 and AATRM trials addressed the question of what to do with sentinel node-positive micrometastases. Yet, micrometastases were rarely detected in axillary nodes prior to the era of the sentinel lymph node biopsy technology. Thus in the previous era, axillary nodes were generally evaluated with routine sectioning and H&E staining. However, pathologists now often undertake a very exhaustive evaluation of the sentinel nodes that includes micro-sectioning and immunohistochemical staining, and thereby uncover micrometastases which might not otherwise have been detected64. Analysis of the NSABP-B32 trial data suggests that the prognosis of patients with micrometastases in the sentinel nodes is similar to that of node-negative patients65. Moreover, macrometastases (but not micrometastases) have been the basis of several clinical trials that have assessed eligibility for adjuvant systemic therapy66. Thus, there appears to be no obvious clinical benefit to identifying micrometastases within sentinel nodes, and the practice of exhaustive histological evaluation of these nodes should perhaps be abandoned65.

The AMAROS and ACOSOG Z0011 trials addressed the issue of what to do with sentinel node-positive macrometastases, which are of greater clinical consequence. In the AMAROS trial, sentinel node-positive patients (macro-/micrometastases) were randomized to either axillary radiotherapy or completion axillary surgery. There was no significant difference between the two arms of the trial in terms of either recurrence or mortality, but the risk of lymphedema was substantially lower in patients treated with axillary radiotherapy when compared to a surgical option. The American College of Surgeons Oncology Group (ACOSOG) Z0011 trial randomized almost 900 SLNB positive patients to either no further axillary surgery or completion ALND. At an initial median follow up of almost 6 years, there was no statistically significant difference between the two arms in terms of loco-regional recurrence or overall survival. This trial recruited node positive patients with macro- or micrometastases and included only breast conservation patients who received breast irradiation - half of whom had high tangent fields which captured some of the nodes in the lower axilla and this may have contributed to non-inferiority. The trial has been criticized for incomplete accrual and patients lost to follow-up. Nonetheless, updated follow up at 10 years reinforced earlier conclusions and revealed no significant difference in rates of axillary recurrence between the observation group (1.5%) and ALND group (0.5%) (p=0.28) with distant disease from survival rates of 80.2% and 78.2% respectively (p=0.32). Patients in Z0011 generally had a low burden of axillary disease with a low likelihood of having >2 nodes positive. Nonetheless, this and the other 3 trials above have confirmed that SLNB has a similar therapeutic value for a selected group of patients undergoing breast conserving surgery. Compared with the era of NASBP B-04, patients now present with smaller tumors with lower nodal burden, knowledge of absolute numbers of positive nodes is less important and systemic therapies provide effective loco-regional control in many patients with minimal tumor load in non-sentinel lymph nodes. None of the aforementioned trials apply to patients treated with neo-adjuvant systemic therapy.

Some investigators have expressed concerns about the ACOSOG Z0011 trial 67-69. It has been argued that the results of this trial are not readily applicable to routine clinical practice. A significant proportion of the patients in this trial had micrometastases of the sentinel node, there was variability in radiotherapy techniques with many patients receiving high tangents that included the axilla, and none were treated with mastectomy. To address these concerns, the POSNOC (Positive Sentinel Node: Observation versus Clearance) trial has been launched in the United Kingdom, Australia, and New Zealand70. This is a pragmatic, randomized, multi-center, non-inferiority trial with a planned sample size of 1900 patients with unifocal or multifocal breast cancer 5 cm or less treated with either breast conserving surgery or mastectomy. Women with one or two positive sentinel nodes (macrometastases) will be randomized to receive either adjuvant systemic therapy alone versus adjuvant systemic therapy and either surgical clearance of the axillary nodes or radiotherapy to the axilla. All patients in this trial will be followed for five years and the primary outcome measure will be axillary recurrence.

**AXILLARY MANAGEMENT IN PATIENTS RECEIVING NEO-ADJUVANT CHEMOTHERAPY**

Management of the axilla in the context of neoadjuvant chemotherapy continues to evolve as response rates increase and more patients undergo this modality sequence71. Before the advent of SLN biopsy all neoadjuvant chemotherapy patients had an ALND as definitive treatment of regional nodes. The pre-treatment status of axillary nodes was unknown and some node positive patients became node negative following primary chemotherapy consequent to nodal downstaging. Therefore, neoadjuvant therapy did not influence surgical treatment in terms of the axillary procedure as ALND remained standard of care irrespective of the primary treatment approach and had minimal impact on adjuvant therapy decisions.

Introduction of SLNB for primary surgical patients permitted omission of ALND in the majority of patients but those undergoing neoadjuvant therapies were obligated to ALND despite a favorable breast tumor response that might render a patient suitable for breast conserving surgery (BCS). A dichotomy of practice emerged in attempts to define how SLNB should be incorporated into the neoadjuvant setting with axillary staging either before initiation of chemotherapy or following chemotherapy with completion ALND as indicated. Prospective data is now available from clinical trials assessing the safety and accuracy of these two approaches.

*Sentinel Lymph Node Biopsy Before Neoadjuvant Chemotherapy (NACT)*

An upfront SLNB prior to NACT minimizes the risk of a false negative result and may allow more accurate initial staging of patients38,72. Identification rates are high (98-100%) as surgeons have much experience of pre-treatment SLNB as part of primary surgery therapy. Likewise, false negative rates are comparable and average 11% in this setting. Node positivity rates vary from 29 – 67% but this reflects a selected patient population with higher stage disease. More recent reports suggest that node positivity rates are lower when pre-operative axillary ultrasound is routinely employed (42 – 45%)73. Completion ALND can safely be avoided at the time of definitive breast surgery when the SLNB is negative with low rates of regional recurrence. Although an upfront SLNB can provide information on prognostication and guide treatment decisions for adjuvant therapies, there is no quantification of regional metastatic load. For example, SLNB may yield a single positive node (1/1) only despite the presence of additional positive nodes at presentation. Knowledge of pre-treatment nodal status potentially influences the decision to give chemotherapy for patients with relatively small tumors and type of chemotherapy (e.g. taxane-based). However, it is decisions for chest wall and supraclavicular radiotherapy which are currently most likely to be influenced by a positive upfront SLNB. A major disadvantage of SLNB before NACT is the requirement for a second operation but this may also be necessary in the event of a positive SLNB post-NACT when facilities for intra-operative node assessment are not available. There are also concerns about possible delays in commencement of definitive treatment (primary chemotherapy) due to scheduling issues and wound complications (chemotherapy should not be started within 4 days of SLNB). Nonetheless, SLNB prior to NACT can be helpful if negative and can reinforce any decision to withhold chest wall or regional nodal irradiation.

*Sentinel Lymph Node Biopsy after NACT*

Increasingly SLNB is advocated after primary chemotherapy to take advantage of potential nodal downstaging and avoidance of ALND in up to 70% of patients in certain subgroups (triple negative and HER2 positive breast cancer)74-76. There is some evidence that primary chemotherapy can modify lymphatic drainage patterns leading to differential downstaging between sentinel and non-sentinel nodes77. Reports have shown false negative rates in the range of 8 – 11% with a pooled estimate of 12% for SLNB following NACT for clinically node negative patients [TABLE 1]77-81. In the NSABP B-27 study, the overall false negative rate was 11% but lower when dual localization techniques with blue dye and radioisotope (8%) were employed compared with blue dye alone (14%)77. The French Ganea study included clinically node negative and node positive patients with false negative rates of 9.4% and 11.6% respectively80. Hunt and colleagues from the MD Anderson Cancer Center found a relatively low false negative rate for SLNB after NACT (5.9%) which was not significantly different from pre-chemotherapy SLNB (4.1%) [p=0.39]81. Rates of complete pathological response (pCR) in patients with needle biopsy confirmed positive nodes pre-chemotherapy range from 20 – 42%. Most metastases diagnosed on needle biopsy are macrometastases [>2mm] and pCR may conceivably be higher for micrometastases. Moreover, patients with a pCR in breast and nodes appear to have a better prognosis and disease-free survival82.

Despite certain theoretical concerns about the intrinsic accuracy of SLNB post-chemotherapy, there is no conclusive evidence for any of the above phenomena compromising the accuracy of SLNB following chemotherapy with an increasing volume of data now supporting the accuracy and popularity of this approach – especially for biopsy confirmed node positive patients at the outset whose clinical status converts to node negative after NACT. This change in practice has occurred pari-passu with improved understanding of multimodality therapy and modulation of loco-regional disease control by adjuvant treatment 83.

Until recently, there were mixed reports on the accuracy of a post-NACT approach for biopsy-proven node positive patients converting to node negativity clinically. Table 2 shows corresponding false negative rates that were initially up to 25% but more recently are in the range 10 – 15% 84-88. Alvarado and colleagues expressed persistent concerns about false negative rates amongst patients presenting with biopsy-proven node positive disease87. They reported an overall false negative rate of 20.8% amongst a group of 150 patients undergoing SLNB post-NACT (of whom 111 had an ALND). The false negative rate was reduced to 16.1% with normalization of nodes on ultrasound following induction chemotherapy and was notably higher when only a single node was retrieved.

The American College of Surgeons Oncology Group (ACOSOG) Z1071 trial examined false negative rates for patient with core biopsy proven node positive breast cancer 89. The trial enrolled almost 700 clinically node positive patients (T0-T4, N1, N2, M0). SLN biopsy was undertaken with dual tracer agents (blue dye and radioisotope) for the majority of patients, but some were localized with a single tracer. All patients received ALND following SLNB and allowed calculation of surgical false negative rates. The primary endpoint for this study was the false negative rate when ≥2 nodes were removed and the pre-defined value was ≤10%. The actual false negative rate when dual tracer agents were used and ≥2 nodes were harvested was higher than this pre-defined value (12.6%) but was less than 10% when at least 3 nodes were removed and pre-operative axillary ultrasound was employed. Patients within the German SENTINA trial were randomized to 4 arms, one of which included clinically node positive patients (n=592) who become clinically node negative after NACT90. The SLN identification rate was a modest 80% and the false negative rate relatively high at 14.2% [95% CI 9.9% - 19.4%] 90. A meta-analysis has recently examined SLNB following NACT in more than 3000 patients with biopsy-proven clinically node positive breast cancer. The pooled identification rate was 91% with an overall false negative rate of 13% and this accords with results of the ACOSOG Z1071 and German Sentina trials91. The adjusted pCR in this meta-analysis was 47% and the false negative rate was lower when both H&E staining and immunohistochemistry were employed for nodal examination. Thus SLNB following NACT for clinically node positive disease is feasible but false negative rates are higher and identification rates slightly lower than for primary SLNB (>95% and 8 – 10% respectively).

*Omission of Completion ALND after Nodal Downstaging*

There is limited data on the consequences of omitting completion ALND in biopsy-proven node positive patients who convert to node negativity clinically and subsequently have a negative SLNB after NACT. There is confounding within some studies due to patients having unscheduled ALND (up to 30%) but rates of axillary recurrence appear low in absolute terms. Thus Hunt and colleagues reported a recurrence rate of only 1.2% at a median follow up of 55 months in this group of patients whilst another group from Italy found no axillary recurrences at a median follow up of 60 months amongst 70 node positive patients with a negative SLNB post-NACT81,92. More information is required on rates of regional recurrence in this setting as these are likely to be higher when there is residual disease in non-sentinel lymph nodes after a false negative SLNB post-NACT; these patients have not responded well to chemotherapy and will not have any further chemotherapy in general (hormone sensitive patients will be treated with endocrine therapy (5 – 10 years) whilst HER2 positive patients will receive trastuzumab). It should be noted that the rationale for omission of ALND in the Z0011 trial would not apply to SLNB positive patients after NACT. The significance of micrometastases [ypN1mi] and/or isolated tumor cells [ypN0i+] in post-chemotherapy patients remains unclear as they may be of different biological importance if representing downstaged macrometastases. Ideally, the response in axillary nodes should be *all or none* rather than a partial response leaving residual disease of uncertain significance. The SN FNAC prospective multicentre study further evaluated the role of SLNB after NACT in biopsy proven node positive patients and found that false negative rates were under 10% with mandatory immunohistochemistry. Thus a sentinel node containing any tumor deposits was considered positive including isolated tumor cells [ypN0i+]; exclusion of IHC detected foci increased the false negative rate to 13.3% Although routine immunohistochemical staining of sentinel nodes in primary surgery is not recommended, this is one situation where it can help reduce false negative rates for SLNB 93. Another issue is whether microscopic disease in sentinel nodes after NACT should determine adjuvant radiotherapy treatment. Any evidence of tumor deposits on H&E staining should prompt completion ALND irrespective of type of breast surgery.

To improve the accuracy and reliability of SLNB following NACT for initially biopsy proven node positive disease, placement of a titanium clip within the axillary node at the time of biopsy is being explored. The clipped node must be retrieved during the surgical procedure of SLNB with evidence that this can ensure false negative rates below the 10% threshold. Caudle and colleagues reported a false negative rate of only 1.4% when the clipped node was examined pathologically compared to 10.1% without [p=0.03]94. Similarly, a subgroup analysis of the Z1071 trial examined the impact of clip placement and retrieval 95. A total of 203 patients had a clip placed in the node at the time of biopsy and the clip location was confirmed in 141 clinically node positive cases which had ≥2 nodes resected at the time of SLNB following NACT. The false negative rate was related to the location of the clipped node and was relatively high when there was no clip (13.4%) or no clip was found (14.3%). In three-quarters of cases (107/141) lay within the SLN biopsy specimen and in one-quarter of cases within the ALND specimen. The corresponding false negatives were 6.8% and 19.0% respectively. Thus retrieval of the clipped node as part of the SLN biopsy specimen is important in terms of minimizing false negative rates and efforts are underway to improve detection of the clipped node at the time of surgery and ensure this is removed with the sentinel nodes (if ‘non-sentinel’). Radioactive seed (Iodine-125) localization at initial node biopsy is one method for aiding identification of the biopsied node but is time consuming and probably impractical within a busy breast service 96.

In summary, an upfront SLNB can be considered in clinically node negative patients when pre-treatment nodal status would impact on choice of adjuvant therapies but otherwise SLNB post-chemotherapy is preferred. Ongoing NSABP-51 and ALLIANCE trials will determine whether post-mastectomy radiotherapy should be based on axillary status before or after chemotherapy 97. There is now great confidence in declaration of a negative SLNB after NACT for node positive patients and withholding completion ALND in selected cases. False negative rates are minimized when dual localization methods are used, at least 3 nodes are removed, nodes are sonographically normal post-NACT and any clipped node is retrieved with the SLNB specimen.

**POTENTIAL FOR OMISSION OF AXILLARY SURGERY IN CLINICALLY NODE-NEGATIVE PATIENTS WITH FAVORABLE TUMOR CHARACTERISTICS**

Improvements in adjuvant systemic therapy and radiotherapy contribute to loco-regional control and this has decreased the therapeutic value of axillary surgery98. The role of axillary surgery for staging purposes is also declining with decisions for adjuvant therapies often based on primary tumor characteristics with emergence of various biomarkers of clinical utility (ER, PR, HER2 and Ki-67)99. Furthermore, Oncotype-DX is increasingly used to refine decision making for ER positive node negative tumors (especially luminal B subtypes)100. Interestingly, within the AMAROS trial, clinical decisions for adjuvant therapies were independent of axillary treatment (radiotherapy versus ALND). It is therefore pertinent to ask how appropriate is axillary surgery in contemporary practice 101? In a systematic review of more than 15,000 patients, rates of axillary recurrence for SLN biopsy negative cases was only 0.3% at a median follow up of 34 months102. Moreover, in the ACOSOG Z0011 trial, the rate of axillary recurrence at 10 years for the SLNB only arm was 1.5% and not significantly different from the slightly lower figure of 0.5% for the ALND dissection arm (p=0.28). So why perform SLNB if there is no survival benefit from ALND, axillary recurrence rates are low and axillary surgery has minimal role in selection of patients for adjuvant treatments 103? Can routine axillary surgery for staging purposes be abandoned in some patients with clinically node negative breast cancer and favorable primary tumor characteristics? It should be noted that there is a finite rate of lymphedema associated with SLNB of approximately 5% at 5 years that has relevance to prolonged survivorship104. Thus although ALND is performed less frequently, the prevalence of lymphedema may be high due to patients living long enough to develop this complication after SLNB. Two ongoing trials are exploring the feasibility of omission of axillary surgery in patients with early stage breast cancer undergoing primary breast conserving surgery. Gentilino and colleagues at the European Institute of Oncology in Milan are conducting the Sentinel node versus Observation after axillary UltrasouNd or SOUND trial [NCT02167490] 105. This is a multicenter non-inferiority trial with an accrual target of 1560 clinically node negative patients of any age with tumors ≤2cm amenable to breast conserving surgery (all with normal axillary nodes on ultrasound or FNAC negative). Eligible patients will be randomized to SLNB (with ALND if sentinel node-positive) or no axillary surgery altogether. The primary endpoint for this trial is distant disease-free survival which is a proxy for overall survival 103,105.

A similar non-inferiority trial with both primary and secondary randomization phases has been initiated from the University of Rostock in Germany and will initially randomize patients to either no axillary surgery or SLNB 106. In the event of node positivity, those with 1 – 3 nodes containing macrometastases will be secondarily randomized to either observation or completion ALND. Patients with ≥4 positive nodes will have mandatory ALND. The primary outcome measure is invasive disease-free survival and this Intergroup-Sentinel-Mamma (INSEMA) [NCT02466737] trial aims to recruit approximately 7000 patients106. It should be noted that the active comparator for the first randomization is SLNB whilst for the second completion ALND.

Before introduction of SLNB into routine practice, there was a policy at the Royal Marsden Hospital in London for withholding ALND in ‘low risk’ post-menopausal women undergoing mastectomy or breast conservation therapy (pre-operative axillary ultrasound was not routinely performed at the time)107. Low risk was defined as ER positive grade I tumors (≤2cm) or grade II tumors (≤1.5cm) without lymphovascular invasion. The overall incidence of node positivity was 13% and the rate of axillary recurrence at a median follow up of 40 months was 1% 107. Longer term follow up of this low risk cohort has recently been published and reveals an overall cumulative incidence of axillary recurrence of 1.9% at 10 years and a rate of 2.7% at 10 years for SOUND eligible patient 108. It therefore seems likely that the observation arm of the SOUND trial will be non-inferior to the standard treatment arm and lead to practice changing conclusions.

**CONCLUSION**

There has been substantial de-escalation of axillary surgery over the past 20 years but this belies the complexity of axillary management with a range of options now existing for staging and therapeutic purposes32. These include axillary lymph node dissection (usually to level II), SLNB, axillary radiotherapy or observation only (in lieu of axillary staging or following initial SLNB). Local and regional control is determined by interdependence of treatment effects, tumor burden and innate biology. In the modern era, axillary surgery must remove a sufficient number of nodes to ensure that any residual axillary tumor burden is adequately managed with adjuvant therapies without compromise of clinical outcomes. More extensive surgery and radiotherapy should be restricted to patients at higher risk of regional relapse, namely those with ≥2 nodes positive. A more conservative approach to axillary surgery will lead to reduced morbidity and gains in quality of life are commensurate with improvements in breast cancer survivorship. Advances in imaging and percutaneous biopsy techniques may lead to abandonment of axillary surgery for routine staging purposes although at the present time there are problems of quantifying nodal burden from non-surgical staging methods.

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**TABLE 1**

**Trials assessing the accuracy of sentinel lymph node biopsy after**

**neoadjuvant chemotherapy**

**STUDY/AUTHOR IDENTIFICATION RATE FALSE NEGATIVE RATE**

**NSAPB B-27 85% 11%**

[Mamounas E, et al. J Clin Oncol 2005; 23: 2694-702]  **(8%** [dye + RI]; **14%** [dye alone])

(428 patients)

**GANEA (French) 90% 11%**

[Classe J, et al. J Clin Oncol 2009; 27: 726-32] **(9.4%** [node -ve]; **11.6%** [node +ve]**)**

(195 patients)

**MDACC 97.4% 5.9%**

[Hunt KK, et al. Ann Surg 2009; 250: 558-66] **(4.1%** [pre-chemotherapy]; p=0.39**)**

(575 patients)

**TABLE 2**

**Accuracy of sentinel lymph node biopsy after neoadjuvant chemotherapy in biopsy proven node-positive patients**

**AUTHOR No. PATIENTS FALSE NEGATIVE RATE**

***Shen* et al. (2007) 69 25%**

***Lee* et al\*. (2007) 238 5.6%**

***Newman* et al. (2007) 54 10.7%**

***Alvarado* et al. (2012) 150 16.1%**

***Boughey* et al. (2013) 649 12.6%**

**[\* FNAC positive or US/PET suspicious]**

**LEGENDS**

**FIGURE 1**

**Anatomy of the Axilla.**  Level I: Axillary nodes lateral to the pectoralis minor muscle; Level II: Axillary nodes posterior to the pectoralis minor muscle; Level III: Axillary nodes medial to the pectoralis minor muscle

**FIGURE 2**

**Overall survival for node-negative and node-positive patients in**

**the NSABP B-04 study according to treatment**

No significant differences were observed among node-negative patients

undergoing radical mastectomy, total mastectomy, and radiation or total mastectomy alone, nor between node-positive patients treated with either radical mastectomy or mastectomy and irradiation. NSABP=National Surgical Adjuvant Breast and Bowel Project.

**(From Jatoi I, Benson JR, Lancet Oncology 2016; 17: e430-e441)**

**FIGURE 3**

**Schematic of progressive de-escalation of axillary surgery**

**(From Jatoi I, Benson JR, Lancet Oncology 2016; 17: e430-e441)**

