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Editorial Comment

Why remove four by chance when one will suffice?

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Breast cancer remains the most common cause of cancer in women and is the second leading cause of cancer death. The surgical management of breast cancer has evolved over the last 40 years from radical ablative procedures to breast conservation as the preferred method of treatment for early stage disease. The presence of axillary lymph node metastases remains the best prognostic indicator for patients with breast cancer and the mainstay of surgical management of breast cancer has included the removal of Level I, II and at times III axillary lymph nodes. The presence of axillary nodal metastases is often used to identify patients who would benefit from adjuvant treatment or a more aggressive adjuvant therapy regimen. However, over the last 10 years, the need for adjuvant therapy has often been based on the primary tumour characteristics and an increasing number of node-negative women are offered adjuvant therapy. This has led some to question the need for axillary surgery.

Several methods have been used to identify breast cancer patients at risk of nodal metastases; however, none has been able to replace the need for histological evaluation of axillary lymph nodes. Fisher and colleagues [1] demonstrated that approximately 35% of nodes considered normal on physical examination contained carcinoma and 25% of enlarged suspicious lymph nodes on examination did not contain metastastic cells; therefore, clinical exam alone is not an accurate assessment of nodal status. Other radiological modalities such as computerised tomography, magnetic resonance imaging and mammography present similar difficulties with respect to determining the tumour status of lymph nodes. Positron emission tomography can identify nodal metastases larger than 1 cm, but its use would have limited value in the majority of patients [2]. In 1955, Berg popularised the anatomical subdivision of the axillary lymph nodes into three functional levels related to the pectoralis minor muscle [3]. Lymph nodes lateral and inferior to the pectoralis minor muscle are classified as Level I nodes, those located behind the pectoralis minor muscle are Level II nodes and nodes superior and medial to the pectoralis minor muscle are Level III nodes. Several types of axillary dissections are therefore defined by the Berg levels removed. A low axillary dissection removes Berg level I nodes, while a partial axillary node dissection removes Berg I and II levels and a total axillary node dissection removes all three Berg levels. Lesser procedures termed axillary sampling refer to the random biopsy of low axillary lymph nodes without anatomical reference [4]. The United States National Institutes of Health Consensus Conference in 1991 recommended that a Level I and II axillary lymph node dissection (ALND) be performed in patients with early breast cancer [5]. This is because axillary staging associated with this procedure is very accurate and has less than a 2% false-negative rate [6,7]. However, the ability to achieve this level of accuracy is at the expense of considerable morbidity: the most devastating to patients is chronic lymphoedema, which has been reported to occur in as many as 20–30% of patients in some series [8–10]. Because only approximately one-third of patients who present with breast cancer have nodal metastases, routine axillary nodal dissection places a substantial number of patients at risk for operative morbidity without any known benefit from the operative procedure. Attempts to reduce the morbidity of axillary node dissection with lesser procedures such as low ALND or axillary sampling have been abandoned due to high false-negative rates. There is a 40% false-negative rate with random axillary nodal sampling and a 10–15% false-negative rate with excision of Level I nodes alone [10–15]. The recent introduction of the sentinel node biopsy (SNB) provides a less invasive, but highly accurate, alternative of axillary assessment to axillary node dissection.

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In this issue, Macmillan and coworkers at the Breast Unit at Nottingham City Hospital report their approach of four-node sampling (4NAS) as an alternative to SNB. In this study, 200 patients with early breast cancer were evaluated using both techniques. The SNB was performed using radioactive colloid alone. 27 MBq 99m-Tc labelled colloid was injected peritumorally prior to surgery. The C-Trak probe was then used to identify the sentinel node (SN) intra-operatively. In the first 15 patients, a lymphoscintogram was used to confirm the location of the SN. At the time of surgery, a standard 4NAS was performed by palpating the low axilla, and the four nodes thought most likely to contain metastatic disease were removed. The 4NAS technique was pioneered in the Edinburgh breast unit and relies on the theory that involved axillary nodes are the ones most likely to be palpable intra-operatively. The lower axilla is mobilised and four nodes are individually identified and removed. On a few occasions, a suspicious node was palpated higher in the axilla and in these rare cases this lymph node was also excised. Each lymph node was then counted using the gamma probe. The gamma probe was then used to evaluate the axilla and if a lymph node was identified with a higher count this was excised as an additional node.

A SN was identified in 96% of cases with a mean of 1.5 SN per patient. A SN was defined as the 'hottest' node, and any nodes at least 25% as 'hot' as the 'hottest' node with at least 25 counts per 10 s were also classified as sentinel. In 153 cases (80%) the SN was part of the 4NAS. However, in 38 (20%) of cases, one or more SN were identified in the axilla after performing the 4NAS. A SN was not identified in 9 patients, 2 of which had a positive axillary lymph node identified with 4NAS. In 8 patients, the SN did not accurately predict the status of the axilla: a false-negative rate of 14%. Overall, 10 patients would have been understaged by SNB and 1 patient would have been understaged by 4NAS if either technique had been used in isolation.

This study attempts to argue that SNB using radioactive colloid has little to offer surgeons who perform 4NAS. However, it is difficult to understand how it is possible to palpate a small micrometastastic tumour deposit in 4NAS! The patients with small metastases usually do not have enlarged nodes. It has already been shown that clinical assessment of the axilla is inaccurate. Does the accuracy increase when direct intra-operative palpation of the lymph nodes is performed? How big does a metastatic deposit have to be in order to be palpated? Can one palpate a 1, 2 or 3 mm metastatic deposit? The authors acknowledge that SNB is still in the early stages of refinement and that it may evolve into a more accurate and clinically useful staging procedure. They feel that the resources and efforts allocated to SNB could be more productively spent in other aspects of breast cancer care! The authors clearly do not support the concept of SNB and will likely need more convincing, despite studies that have shown nearly 100% correlation between SNB and axillary dissection.

There are several flaws in this study that should be elucidated. The authors should be congratulated on their success rate at identifying the SN. They identified the SN in 96% of cases; however, the false-negative rate was 14% which is a high rate even when compared with the Multicenter Validation study which had a false negative rate of 11% [16] In 1997 we published our results of 107 patients undergoing SNB followed by ALND in which the false-negative rate was 0% [17]. Part of the problem with the current Nottingham study was likely related to technical issues. The SN in this study was identified using a pre-operative injection of 0.3 ml of 27 MBq 99m-Tc labelled colloid. This small volume of colloid most likely limited the ability to successfully identify the SN. Others have reported success using a higher volume of fluid in the breast with the injection of six 1-ml aliquots in separate sites at the periphery of the tumour or at the site of the previous excisional biopsy [18].

The most significant flaw in this study, however, relates to the ability to prove the accuracy of either technique. The authors did not perform a standard ALND in each patient; therefore, there is no way to determine the true accuracy of either technique. An ALND was only performed if the SN or a node in the 4NAS was found to be positive and the patient was undergoing further surgery to the breast. Otherwise, an ALND was not performed and the patient was given radiation therapy to the axilla. The authors compare the accuracy of SNB to 4NAS based on the ability to find a positive SN in each technique, but this is not a true assessment of the accuracy of the techniques. A standard ALND should have been done in each case in order to get the true false-negative rate for each technique. Furthermore, if either technique truly identifies a patient with a tumour-free axilla, why irradiate the axilla and subject the patient to the significant morbidity of axillary radiation?

The authors imply that a SNB would add to the cost of the surgery unlike a 4NAS; however, the cost of a SNB is debatable. Although it is true that there is considerable added expense with the use of radioactive colloid, the cost of a blue dye is negligible. In addition, one could argue that a SNB could be done under a local anaesthetic rather than the general anaesthetic which is needed for 4NAS, which would significantly reduce the cost of the surgical procedure.

The authors argue that a SNB does not give sufficient prognostic information. They argue that a patient with a positive SN will require a second procedure to obtain sufficient prognostic information. This may be true if

metastases are not identified at the time of surgery. This occurs in approximately 20% of cases in which the frozen section of the SN is negative, but permanent section analysis identifies metastases [19]. This would also be true in 4NAS. The authors did not perform frozen sections on the SN or lymph nodes from the 4NAS and therefore a second operation was needed in their subset of patients as well. A SNB is performed in order to identify a subset of patients with lymph node metastases. The majority of patients do not have metastases at the time of initial diagnosis. This group of women could be spared the morbidity of an ALND. However, the more important question is: Is an axillary dissection therapeutic? Does it impact survival or is it merely a staging procedure? The patients who have sentinel node metastases at this time do proceed to a Level I and II axillary dissection in order to sufficiently evaluate the axilla. Many times, the SN is the only lymph node to contain metastatic disease. However, there are no predictable criteria to determine in which patients this will occur. Therefore it is difficult to determine which SN-positive patient may avoid an ALND. We encourage our SN-positive patients to participate in the American College of Surgeons Oncology Group Study Z0011 that randomises patients with a positive SN to an ALND or observation. This study will finally answer the question of whether an axillary dissection is prognostic or therapeutic.

This Nottingham study demonstrates the feasibility of 4NAS in their centre. This study attempts to demonstrate the superiority of this staging procedure compared with SNB. The comparison is flawed, but more investigation is needed. Intellectually, it is unlikely that intra-operative palpation or random excision will be more accurate than the SNB, which relies on demonstrating the lymphatic subanatomy of the breast. This technique may be difficult to master, but once the surgeon is experienced it is likely to be more reliable than palpation or chance, especially since most metastases are small in the patients with early breast cancer who would undergo this operation. The high level of accuracy of SNB has been demonstrated not only by our group, but other experimental centres in the US and Europe [17,18,20–21]. SNB is here to stay and will likely replace ALND in node-negative women and may even replace ALND in node-positive women. It is not evident that by removing four lymph nodes the ability to detect metastases improves. We would argue that a more directed, anatomical approach to the axilla, as is the case with the SNB is likely to be a more accurate method to evaluate the axilla. Why remove four when one will suffice?

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