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REVIEW ARTICLE

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Pathological assessment of sentinel lymph-node biopsies in patients with breast cancer

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The extent of axillary surgery in patients with breast cancer remains a controversial subject. In patients with invasive carcinoma of the breast, surgery to both the breast and the axilla has become less extensive. Radical mastectomy, in which the pectoral muscles and the breast are removed, has been replaced by simple mastectomy or wide local excision, with no increase in mortality. Traditionally, axillary clearance was performed; now, many surgeons perform axillary-node sampling or low axillary clearance. The most recent surgical innovation is axillary sentinel-node biopsy, which is an even less extensive procedure.

There are three potential reasons for axillary surgery. Staging and reduction in axillary recurrence are of proven value; the effect on survival is uncertain. The main value of axillary surgery is as a staging procedure. Pathological examination of axillary nodes is essential, as clinical assessment is unreliable [10, 13, 47]. Indeed, pathological axillary-node status, histological grade and tumour size are the three most powerful pathological predictors of survival in stage-I and -II disease [12, 19] and are important factors in decisions about adjuvant treatment.

Axillary-node sampling and low clearance may under-stage the axilla, but there is no consensus on the number of nodes that should be examined to ensure accurate staging. It is clear that the larger the number of lymph nodes involved, the worse the prognosis [14], and there is some evidence that the anatomical level of involvement is also important [6, 55]. Some studies have found that the proportion of "negative" axillas declines as more nodes are sampled [2, 33 34], but this is not a consistent finding [13]. Such a relationship could be interpreted as implying that more nodes should be sampled, but involved nodes may be easier for the surgeon and pathologist to identify. Another consequence of under-staging of the axilla with axillary sampling is an increased incidence of ipsilateral axillary recurrence in patients thought to be node negative, particularly if fewer than five nodes are examined [2, 24]. In Edinburgh, sampling of four axillary nodes was as good an indicator of whether the axilla was involved as full axillary clearance [51], but others have found a false negative rate of 12–14% for axillary sampling [10, 31].

A potential explanation for some cases of under-staging with axillary sampling or low axillary clearance is that there are metastases to level-2 axillary nodes, with no involvement of the low (level-1) nodes. Such "skip" metastases have been shown in 1–30% of node-positive patients [4, 45, 47, 49, 54]. Part of this wide variation can be explained by the fact that the studies with higher figures had more nodes removed at level 2 than at level 1 whereas, in most studies (and in our experience), there are more nodes at level 1.

As noted above, axillary clearance also reduces the risk of regional recurrence. With no surgery or radiotherapy to the axilla, the risk of axillary recurrence is approximately 20% [13, 15, 24, 26]. After complete axillary clearance, the risk of recurrence is approximately 2% [3, 15]. This benefit of axillary clearance affects patients with positive nodes, particularly those with more than four nodes involved. There are conflicting results about the recurrence rate after axillary-node sampling and the role of radiotherapy. Overall, axillary clearance is over-treatment for many patients who have negative nodes.

There is no definite evidence that axillary surgery improves survival [43]. Thus, the benefits and extent of axillary surgery must be counterbalanced by the complications of the procedure, particularly lymphoedema of the arm, neuropathy and restricted shoulder movement [30].

The principle of sentinel lymph-node biopsy is that the first lymph node to which the tumour drains is the site of the first lymphatic metastasis. Whether the sentinel lymph node is involved or not should, therefore, reflect the status of the group of nodes. If the sentinel lymph node is positive, then further surgery or radiother-

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apy can be performed. If it is negative, the remaining nodes in that group should also be uninvolved. This concept was initially tested in carcinoma of the penis and then in malignant melanoma before being investigated in carcinoma of the breast. The average size of mammary carcinoma at presentation is decreasing, particularly due to mammographic screening, and the proportion of women who have negative axillary nodes is approaching 70%. A major attraction, if the concept is valid in patients with carcinoma of the breast, is that, if the sentinel node is free of tumour, then axillary clearance can be avoided in the majority of women. The advantage of reducing the extent of surgery is lower in centres (such as ours) that use axillary-node sampling.

Several studies have shown that, if only one node is involved with metastatic carcinoma, it is almost always the sentinel node; the sentinel node is frequently the only site of metastasis. One weakness of some of these studies is that the sentinel node is examined more intensively than the other nodes, which may mean metastases in non-sentinel nodes are missed [5, 22, 23, 52, 57]. Nevertheless, there are sufficient studies without this bias that the sentinel node concept has been validated for the axilla in breast cancer [1, 21, 41, 46].

There is no consensus on the best method of identifying the sentinel lymph node(s). The two main methods use either a blue dye [21] or a radiolabelled material [32, 41, 56]. In both methods, the dye or radiolabelled material is injected around the tumour or deep into the overlying skin. In the dye method, the location of the sentinel node is not known preoperatively, and the blue-stained lymphatics are followed to the sentinel node intraoperatively. Therefore, the surgical incision may need to be large. The timing of the surgery has to be accurate, because the dye can pass through the sentinel node so that the true sentinel node may be missed. The radiolabelled material can be detected with lymphoscintigraphy, intraoperative γ-probe or a combination of the two. With lymphoscintigraphy, the sentinel lymph node can be detected preoperatively. This has the advantage that sentinel lymph nodes outside the axilla (such as in the internal mammary chain) can be identified, and the operative incision can be located more accurately. Some suggest that a combination of the two methods is best [1, 8, 42]. All methods have a learning curve [21, 41]. However, with experience, the proportion of patients in whom the sentinel node is identified is 93–99% in most recent large studies [5, 8, 23, 57], although the figure is nearer 80% in some [41].

The findings in the sentinel lymph node have been compared with those for the remaining nodes in immediate axillary clearance. The proportion of false-negative sentinel lymph nodes [sentinel lymph node(s) negative, with metastases elsewhere in the axilla] varies from 1% to 11% in the larger series [5, 23, 32, 41, 57]. It has not been determined whether this false-negative rate is acceptable to clinicians or their patients. There are also many unresolved issues regarding which patients should be considered for sentinel lymph-node biopsy. The false-negative rate may vary with the characteristics of the primary tumour. Some have suggested that the false-negative rate is particularly low for small tumours [20, 56]. A counter-argument is that this group might not require adjuvant therapy if the tumour size is less than 10 mm and the nodes are negative – to miss nodal metastases in these patients would deny them the potential benefit of adjuvant therapy. Reduced rates of detection of sentinel lymph nodes have also been described in multicentric tumours [20], patients with prior excision biopsy [32] and with medial tumour location [32]; thus, these may be contraindications for the technique. Most studies have investigated patients with a clinically negative axilla, but it is questionable whether the technique should be restricted to such patients, particularly since clinical assessment of the axilla is unreliable.

Sentinel lymph nodes are usually in level-1 axillary nodes, but sentinel nodes in level-2 nodes are seen in between 0% and 23% of patients [1, 5, 21, 32, 46]. The division of axillary lymph nodes is based on anatomical relationships (to the pectoralis minor) rather than on function. Thus, “skip” metastases (for example, to level-2 axillary nodes) may be the result of anatomical variations in lymphatic pathways. We have seen metastasis to an intramammary lymph node from a tumour in the upper outer quadrant, while the axillary lymph nodes detected with a γ-camera were not involved.

Sentinel lymph nodes at extra-axillary sites are not addressed in most studies. Occasionally, hotspots are detected in the internal mammary or supraclavicular regions but, in contrast to the axilla, these have usually not been assessed pathologically [5, 32, 46, 50]. Therefore, the sentinel-node concept has not been tested for extra-axillary nodes in breast cancer.

The pathological method used to assess the sentinel node is of central importance. The evidence that axillary-node status is a prognostic factor is largely based on studies in which one section from each axillary node was examined using haematoxylin-and-eosin-stained sections. Additional laboratory techniques can be used to increase the sensitivity of detection of metastases. Complete, separate embedding of each node and serial step sectioning increase the chance of identifying metastases as more of the node is examined [29, 38, 59]. Immunohistochemistry also increases detection [25, 35, 38], in part by making the metastases easier to see. Reverse transcriptase polymerase chain reaction (RT-PCR) uses a very sensitive method to examine all the tissue submitted [40, 48]. These additional techniques are only relevant to node(s) that are deemed negative by conventional histological examination. The role of these more sensitive methods in detecting such occult metastases or micrometastases is, at present, controversial.

There have been a number of previous studies looking at micrometastases or occult metastases in axillary-clearance specimens. There are two main problems: first, there is no agreed definition of occult metastases; second, their significance is uncertain. Definitions include metastases less than a given size (such as 2 mm), metas-

tases found on review of the original sections that were initially missed, metastases shown only by taking deeper sections and metastases shown by immunohistochemistry for cytokeratins. There is some evidence that the size of the deposit is of prognostic significance [7, 17, 28, 35, 38, 44]. Serial sections and immunohistochemistry do increase the sensitivity of detection; in 10–20% of patients with axillary specimens that are negative using conventional methods, occult metastases can be shown. In univariate analyses, most of the larger studies with good follow-ups have shown a worse prognosis for patients with micrometastases compared with node-negative patients [11, 25, 29, 35, 38], though the effect is more clear for disease-free survival than for overall survival. What is less certain is the magnitude of this effect after traditional features of the primary tumour (including histological grade, size, lymphovascular invasion and histological type) have been considered in a multivariate analysis.

Using immunohistochemistry, micrometastases, which have not been shown in routine haematoxylin-and-eosin sections, are more frequently shown with invasive lobular carcinoma than with invasive ductal carcinoma [11, 35]. The deposits in invasive lobular carcinoma are frequently single cells, and it has been suggested that such metastases have less prognostic significance than the (usually larger) metastatic deposits in invasive ductal carcinoma [11]. There is conflicting data on whether the position of the metastasis (in the marginal sinus or parenchyma) is important [18, 27, 29, 59]. Not surprisingly, immunohistochemistry and serial sections also increase the detection of metastases in sentinel lymph-node biopsies [9, 55]. Such occult metastases are more common in sentinel nodes than in non-sentinel nodes, further validating the sentinel-node concept [58]. However, the prognostic significance of such occult metastases is unknown. Indeed, there are no prospective prognostic studies of occult metastases in either sentinel lymph-node biopsies or conventional axillary specimens.

RT-PCR is even more sensitive than immunohistochemistry at detecting metastatic tumours [40, 48]. Two types of method can be used to detect tumour cells with molecular techniques. First, a genetic defect, such as chromosomal rearrangement or mutation, can be identified. The problem with this is that no single genetic defect is seen in all breast carcinomas. The second method is based on a molecular marker that is transcribed by tumour cells but not by the adjacent tissue. To obtain a marker that has this specificity and is expressed in the majority of tumours is difficult. It may be necessary to use a panel of markers. A major problem with PCR is false positive results due to the high sensitivity of the method. In addition, with PCR, it is not possible to determine whether the DNA comes from a viable cell or not. An advantage of haematoxylin and eosin sections and immunohistochemistry is that the morphology of the cells can be examined and malignancy confirmed. A major unresolved question is whether carcinoma detected only by PCR is of prognostic significance. In the only study of prognosis in breast cancer [37], there were only small numbers of patients with breast cancer and, in the analysis of the prognosis, they were combined with patients having gastrointestinal cancer.

The choice of method used to assess lymph nodes must be based on solid evidence. We currently cut all axillary lymph nodes (whether they are sentinel nodes or part of an axillary sample or clearance) into slices about 3 mm thick (taken perpendicular to the long axis to maximise the assessment of the marginal sinuses), with one node per cassette. We find that the majority of nodes can be completely embedded in one cassette. Larger nodes have alternate slices embedded. Very large, obviously involved nodes have one section taken. This approach is consistent with National Health Service Breast Screening Programme recommendations [39]. At present, we feel that more data are required before immunohistochemistry, serial sections or RT-PCR can be advocated for routine use. We also believe that, in studies comparing sentinel lymph-node biopsy with axillary sampling or clearance, all nodes should be examined in the same way to prevent biased comparisons.

Intraoperative frozen sections or imprint cytology of axillary lymph nodes have been advocated by some authors. Conventional frozen sections, we believe, have an unacceptably high false-negative rate of 10–30% [16, 20, 53, 57]. More intensive intraoperative assessment with serial sections and immunohistochemistry has been described [54], but this is time consuming and labour intensive. Frozen sections might be appropriate in selected cases; for example, if the node is macroscopically abnormal and this is confirmed histologically to be metastatic carcinoma, further axillary surgery can be performed immediately. Some studies have found low false-negative rates of 2–3% with intraoperative imprint cytology [16, 46], but not all have been able to achieve this level of accuracy [53]. Most breast carcinomas can be diagnosed preoperatively, and we very rarely perform frozen-section diagnosis of the primary tumour. Our feeling is that frozen section and imprint cytology assessment of axillary nodes is also inappropriate. An alternative approach would be for the patient to have the primary carcinoma diagnosed with core biopsy or fine-needle aspiration cytology followed by sentinel lymph-node biopsy under local anaesthetic. Surgical management of both the breast and axilla could then be planned prospectively.

The traditional “Halsted” view of breast cancer was that there was a logical, sequential pattern of spread of the carcinoma, and this was used to justify radical surgery. More recently, it was proposed by Fisher [13] and others that carcinoma of the breast is often disseminated at the time of diagnosis and that nodal metastases are merely a marker of systemic disease. Associated with this philosophical change is a trend towards less radical surgery of both the breast and the axilla. Thus, axillary sentinel lymph-node biopsy is a reversion to the “Halsted” philosophy while at the same time continuing the trend towards less radical surgery. In reality, the truth probably lies somewhere between the “Halsted” and “Fisher” models. We believe that there needs to be fur-

ther research before sentinel lymph-node biopsy can become part of the standard treatment of breast cancer. In particular, two central questions require answers from clinical trials (1) whether patients with a negative sentinel axillary lymph node(s) can safely avoid further axillary surgery and (2) the clinical significance of micrometastases. Of critical importance to both these questions is the way the pathologist should assess the node biopsy and, thus, how negative and positive nodes are defined. Studies to address these issues are planned [36]. The cost in time, equipment and consumables for sentinel-node biopsy and other forms of axillary surgery needs to be compared. In addition, comparison of the effectiveness of sentinel-node biopsy and axillary-node sampling needs to be addressed, and this is part of the UK ALMANAC study. Because of these many unresolved issues, it is our view that, at the present time, sentinel lymph-node biopsy should only be performed as part of a clinical trial.

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