



Editorial

Reconsidering axillary surgery for early breast cancer

Historical background

For about 125 years, the surgical treatment of breast cancer has been closely intertwined with axillary surgery¹. The bond between breast surgery and axillary surgery had its origins in the 19th century when Rudolf Virchow, a German pathologist, undertook meticulous autopsy studies and reported that women who died of metastatic breast cancer generally had metastasis to the ipsilateral axillary lymph nodes². Virchow postulated that lymph nodes served as the nidus for the distant spread of breast cancer. Soon afterwards, William Halsted, an American surgeon, incorporated Virchow's hypothesis into clinical practice and promulgated the radical mastectomy, whereby the breast, pectoralis muscle and ipsilateral axillary lymph nodes were extirpated *en bloc*¹. If the Virchow/Halsted hypothesis was indeed correct, then the radical mastectomy should have cured patients with node-negative cancers, but long-term follow up of these patients showed that approximately 30 per cent eventually died of metastatic disease². These recurrences in node-negative patients led many investigators to question the notion that lymph nodes served as the sole conduit for the distant spread of breast cancer.

According to the Virchow/Halsted concept, metastasis to the axillary nodes was simply an indicator of tumour chronology. Thus, metastasis to the lymph nodes was believed to be a manifestation of delay in diagnosis. The better prognosis of node-negative tumours was attributed to timely resection, before metastasis to the axillary nodes had occurred. Yet, we have reported that patients who initially present with node-positive breast cancers will experience a shorter interval from first relapse to death when compared to patients who present with node-negative cancers³. Moreover, the extent of nodal metastasis

at initial diagnosis predicts the length of the interval from first relapse to death (*i.e.*, the greater the number of involved nodes at initial diagnosis, the shorter the interval from first relapse to death). Thus, nodal status appears to be an indicator of tumour biology, with node-positive cancers having a more aggressive tumour phenotype. The notion that nodal metastasis is simply a manifestation of tumour chronology (*i.e.*, delay in diagnosis) is therefore, no longer tenable.

Two large randomized trials were undertaken in the United Kingdom and the United States to test the tenets of the Virchow/Halsted hypothesis. In the King's/Cambridge (United Kingdom) and National Surgical Adjuvant Breast and Bowel Project (NSABP)-04 (USA) trials, women with primary breast cancer were randomized to either early or delayed treatment of the axilla (*i.e.*, treatment with either surgery or radiotherapy)^{4,5}. Both trials demonstrated that the delayed treatment of the axilla did not adversely affect mortality. Thus, metastasis to the axillary nodes did not seem to be a prerequisite for the distant spread of breast cancer, and blood-borne metastasis (rather than nodal metastasis) appeared to play a more important role in determining outcomes. Yet, despite the results of these trials, axillary surgery remained an integral component of the surgical treatment of breast cancer for the remainder of the 20th century⁶.

There were two important reasons for the enduring relevance of axillary surgery until the end of the 20th century. First, although both the King's/Cambridge and NSABP-04 trials showed that neither axillary surgery nor axillary radiotherapy reduced breast cancer mortality, these procedures substantially lowered the risk of axillary recurrences (*i.e.*, from about 20% to 2%)^{4,5}. Thus, axillary local therapy was considered essential to reduce the risk of axillary recurrences. Second, during

the later years of the 20th century, adjuvant systemic therapy was widely implemented in the management of early breast cancer, and eligibility for such therapy was often predicated on nodal status⁷. Patients with node-positive breast cancer derived greater absolute benefit from adjuvant systemic therapy than did those with node-negative breast cancer. While either axillary surgery or axillary radiotherapy was equally effective in lowering the risk of axillary recurrence, only axillary surgery provided prognostic information that could be applied to determine eligibility for adjuvant systemic therapy.

De-escalation of axillary surgery

Since the beginning of the 21st century, there has been a dramatic shift in our thinking about axillary surgery and a rapid de-escalation in the application of axillary surgery for the management of patients with clinically node-negative breast cancer⁸. Four factors have contributed to this de-escalation. First, the concept of sentinel node biopsy was introduced, and complete axillary dissection was largely reserved for sentinel node-positive patients^{9,10}. Second, decisions concerning administration of adjuvant systemic therapy have increasingly been predicated on biomarkers [oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER-2) status], and nodal status has become less relevant with regard to adjuvant therapy decision-making¹¹. For instance, axillary surgery is now often entirely omitted in elderly patients with ER-positive tumours¹². Such patients are treated with local therapy of the breast followed by endocrine therapy, and axillary surgery provides very little therapeutic or decision-making value for these patients. Third, randomized trials have demonstrated that a potentially low burden of axillary disease can be safely treated with adjuvant systemic therapy and radiotherapy, often avoiding the need for a complete axillary dissection even in patients with sentinel node-positive tumours^{13,14}. Although the King's/Cambridge and NSABP-04 trials had shown that in the absence of axillary local, the risk of axillary recurrences was 20 per cent, such high rates are not evident today, with the availability of modern adjuvant systemic therapy¹⁵. Finally, there has been a greater use of neoadjuvant systemic therapy in recent years, potentially resulting in substantial downstaging of large breast tumours before surgery, thereby reducing the need for extensive axillary surgery¹⁶.

Thus, in recent years, the role of axillary surgery in the management of patients with primary breast cancer has diminished. However, it should be emphasized that the trend in de-escalation of axillary surgery has applied only to those breast cancer patients who are clinically node negative at the time of surgery. For those patients who are clinically node positive at the time of surgery (*i.e.*, with clinical evidence of axillary disease), axillary surgery (*i.e.*, formal axillary clearance) remains the standard of care.

Potentially avoiding axillary surgery

These developments raise important questions. Can we potentially avoid axillary surgery altogether (and perhaps even omit sentinel node biopsy) for a wider spectrum of patients with primary breast cancer? Although axillary surgery is now often entirely omitted in elderly patients, can it also be avoided in younger patients? This possibility is now being addressed in a large randomized prospective trial underway in Italy, the Sentinel node versus Observation after Axillary Ultrasound (SOUND) trial¹⁷. In this trial, patients of any age with small breast tumours (2 cm or less) who are clinically node negative and who are candidates for breast-conserving surgery will undergo further assessment of the axilla before surgery (with ultrasound and, as indicated, with fine needle aspiration cytology of any single suspicious axillary lymph node). Patients with no evidence of axillary disease on pre-operative assessment will then be randomized to sentinel node biopsy versus no axillary surgery. This is a non-inferiority trial that aims to recruit 1560 women (780 in each arm), with the primary endpoint being disease-free survival.

The de-escalation of axillary surgery has certainly improved the quality of life for many breast cancer patients. Indeed, there are small but potentially serious risks associated with axillary surgery, including the risk of axillary pain, numbness or paraesthesias, poor cosmetic outcomes and arm swelling (lymphoedema)¹⁸. Sentinel node biopsy alone (rather than complete axillary lymph node dissection) substantially reduces these risks but does not completely eliminate them. Thus, a key principle of bioethics, '*primum non nocere*' (*i.e.*, first do no harm), should apply when one considers the utility of axillary surgery/sentinel node biopsy in the modern clinical setting. Today, because of the availability of effective adjuvant systemic therapy and adjuvant radiotherapy, axillary surgery probably has very little benefit in reducing risk of axillary recurrences in patients who present with a low burden of axillary

disease. Moreover, it provides very little information for the adjuvant systemic therapy decision-making process as this is now largely predicated on biomarkers. Therefore, axillary surgery might not be justifiable for many patients who present with early breast cancer. In many instances, the potential risks of axillary surgery may now outweigh its potential benefits.

Conclusion

Further de-escalation of axillary surgery should continue to be based on the results of randomized trials, and the ongoing SOUND trial is an important step in that direction. However, to date, the major axillary surgery trials have been conducted in western countries where breast cancer patients often present with a low burden of axillary disease. It is unclear whether the results of these trials can be extrapolated to countries such as India, where the clinical setting is often very different¹⁹. Although the axillary surgery trials may be internally valid, their external validity (generalizability to other populations) remains a concern. The generalizability of the axillary surgery trials will remain an important issue in the years ahead as we work to not only lower the burden of breast cancer mortality throughout the world but also improve the quality of life for those afflicted with this disease.

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