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Overexploring and overtreating the axilla

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Introduction

There have been concerns about overtreating the axilla in women with breast cancer at least since publication of the NSABP B04 randomized trial in 1977 [1]. This trial showed that variations in locoregional treatment – including whether or not axillary lymph node dissection (AD) was performed in clinically node negative patients – had no influence on survival. NSABP B04 has had a major influence on surgical approaches the breast, and may be considered a precursor to trials, published in the succeeding decade [2,3], that established breast-conserving surgery (quadrantectomy, lumpectomy) as standard treatment for early breast cancer.

As regards the axilla, although AD could be associated with significant morbidity (lymphedema, pain, nerve damage, etc.) moves to a more conservative surgical approach were hampered by the fact that axillary lymph node status was the most important predictor of long-term survival in breast cancer patients and hence an important guide to further treatment [4]. This problem can be considered to have been solved by the development of sentinel lymph node biopsy (SNB) in the 1990s [5]. SNB is a minimally-invasive procedure with fewer side effects than AD which accurately stages the axilla. It therefore provides reliable information to guide subsequent treatment yet safely permits avoidance of AD in the considerable proportion of patients with negative axillary sentinel nodes (SNs) [6–12].

Currently SNB is the standard approach to the axilla in most breast cancer patients with a clinically negative axilla [13]. In particular SNB is recommended for all such patients except those with T3-T4 disease and inflammatory breast cancer, regardless of whether they are scheduled for mastectomy or breast-conserving surgery [13]. Sentinel nodes can be detected in over 97% of cases, and their status predicts axillary status with about 90% accuracy; furthermore the axilla is site of first failure in less than 1% of cases that undergo SNB without AD [14]. For women with a clinically positive axilla – usually verified by preoperative ultrasound-guided needle biopsy [15] – AD is still the standard treatment. Nevertheless there are a number of situations in which the standard axillary management policy can be considered overtreatment or in some cases overexploration. These are discussed in the present review.

Axillary dissection when sentinel nodes are micrometastatic

The development of SNB was accompanied by the use of more exhaustive methods for pathologically evaluating the removed SNs, so as to reduce the probability of missing disease present in those nodes [16]. This resulted in the frequent identification of both micrometastatic foci (≤2 mm) and isolated tumour cells (ITCs) whose prognostic significance was uncertain. Some studies reported that the presence of ITCs and micrometastasis in the sentinel node was associated with worsened prognosis. For example the Dutch MIRROR cohort study investigated the effect of micrometastases and ITCs (in both sentinel nodes and non sentinel nodes) on disease-free survival in patients who received SNB and had favourable tumour characteristics [17]. The study found that five-year disease-free survival in patients with ITCs or micrometastases, who did not receive adjuvant systemic therapy, was significantly worse than in those with no nodal metastases and also did not receive adjuvant systemic therapy. Other comparisons indicated that adjuvant systemic therapy was able to counteract the negative effect of ITCs/micrometastases. In particular both patients with ITCs and those with micrometastases had a gain in five-year disease-free survival of nearly 10% if these received adjuvant systemic treatment.

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Another Dutch study [18] investigated the effect of not performing AD in patients with ITCs or micrometastases in the sentinel node. The authors examined all patients in The Netherlands with invasive breast cancer who had SNB before 2006, favourable tumour characteristics, and either no disease, ITCs or micrometastases in the sentinel nodes. Compared with patients who had AD, adjusted hazard ratios for regional recurrence were 1.08 (95% CI 0.23–4.98) in those with negative sentinel nodes, 2.39 (95% CI 0.67–8.48) in those with ITCs, and 4.39 (95% CI 1.46–13.24) for micrometastases. The authors recommended "axillary treatment" for patients with SN micrometastases and unfavourable tumour characteristics.

The prospective International Breast Cancer Study Group 23-01 trial [19] was designed to determine whether AD was overtreatment in patients with only micrometastases in the sentinel nodes. It was a multicentre, randomised, non-inferiority, phase 3 trial comparing disease-free survival in two groups of breast cancer patients (no AD vs. AD) found to have only micrometastases in the sentinel nodes. After a median follow-up of 5.0 years (interquartile range 3.6–7.3 years), five-year disease-free survival was 87.8% (95% CI 84.4–91.2) in the no AD group and 84.4% (80.7–88.1) in the AD group (log-rank $p = 0.16$). Disease-free survival in the no AD group was non-inferior to that in the AD group (HR 0.78, 95% CI 0.55–1.11; non-inferiority $p = 0{\cdot}0042$). These findings showed that, for patients receiving breast-conserving surgery – most of whom also received radiotherapy (97%) and systemic treatment (96%) – and found to have only micrometastases in the sentinel nodes, AD is not necessary and is therefore overtreatment. The trial also recruited patients who received mastectomy (9% of total) and the results suggested that no AD might also be acceptable in patients undergoing mastectomy, provided the invasive component of the breast lesion was small.

Treatment guidelines now indicate that AD can be safely omitted in patients with micrometastatic disease in sentinel nodes [13,20]. The more recent guidelines also recommend no AD when only ITCs are present in sentinel nodes [13]. This recommendation is based mainly on the results of the large Z0010 [21] and NSABP B-32 trials [22] which investigated the presence of occult sentinel node metastases in patients receiving breast-conserving surgery, SNB, and whole breast irradiation. The NSABP B-32 trial [22] evaluated sentinel nodes that were initially negative for micrometastases and ITCs. On extensive re-examination they found ITCs in 11.1%, micrometastases in 4.4%, and macrometastases in 0.4%. Occult metastases were associated with a small but significant 1.2% decrease in 5-year overall survival, 2.8% decrease in disease-free survival, and 2.8% decrease in distant disease-free survival. It was concluded, however, that these reductions were small and not clinically important, so that ITCs should not be actively sought (for example by immunohistochemical examination) and by implication, when found did not justify AD.

AD must be therefore considered overtreatment in patients with sentinel node micrometastases and ITCs provided they receive adjuvant treatment in accordance with the current recommendations for each intrinsic subtype of breast cancer [20,23].

Axillary dissection when sentinel node involvement is macroscopic but limited

Studies discussed above called into question the need to perform AD when sentinel nodes are minimally involved. The much earlier NSABP B04 [1] had shown that performing or not performing AD in clinically node negative patients had no influence on survival. The Z0011 [24] study was the first randomized trial in the SNB era to investigate the necessity for AD in patients with macroscopic involvement of the sentinel nodes. The trial recruited 891 patients with clinical T1-T2 breast cancer, a clinically negative axilla, and 1–2 involved SNs. All patients received lumpectomy and tangential whole-breast irradiation. Those with macrometastatic sentinel nodes were randomized to either AD or no further axillary treatment. This was a non-inferiority trial with overall survival as primary endpoint. Clinical and tumour characteristics were similar in the AD and no AD arms; 96% of patients received chemotherapy, hormonal therapy or both. After a median follow-up of 6.3 years, five-year overall survival was 91.8% (95% CI, 89.1%–94.5%) in the AD arm and 92.5% (95% CI, 90.0%–95.1%) no AD arm. Thus, no AD alone did not result in inferior survival compared to AD; furthermore axillary recurrence rates were low in both groups (0.9% in the no AD group; 0.5% in the AD group; $p = 0.45$). These findings indicate that for women with cT1-T2 primary and 1–2 macroscopically involved sentinel nodes who undergo breast-conserving surgery, whole-breast irradiation and systemic therapy, AD is overtreatment. However these findings do not apply to patients with T3 disease or worse, more than 2 involved sentinel nodes, extranodal extension, or those scheduled for mastectomy, partial breast irradiation, or neoadjuvant chemotherapy.

An early criticism of Z0011 came from the University Hospital Basel, Switzerland [25]: a review of their cases from 2003 to 2009 indicated that application of Z0011 criteria would have led to omission of AD in less than 10% of patients who received SNB, thus the clinical applicability of Z0011 was limited. However subsequent studies indicated that most women scheduled for breast conserving surgery with sentinel node metastases have limited sentinel node involvement and are candidates for no further axillary treatment [26,27]. Limited data from North America indicate a substantial reduction in performing AD after the publication of Z0011 compared to before publication [28]. Data also suggest that more patients scheduled for mastectomy with positive sentinel nodes are not receiving AD [29].

Further evidence that AD is overtreatment was provided by long-term results of the INT09/98 trial [30], which started in the pre-SNB era. The trial recruited patients, age 30–65 years, with clinically T1N0 disease, randomizing them to quadrantectomy with or without AD, in all cases followed by radiotherapy to the residual breast only. Five hundred seventeen patients were evaluated. After a median follow-up of nearly 11 years (127.5 months; interquartile range 113–141 months) neither overall nor disease-free survival differed between the AD and no AD arms. Although overt axillary disease occurred in 22/245 (9.0%) of no AD arm patients (a median of 30 months after surgery) this had no effect on survival outcomes. The authors commented noted that the biological characteristics of primary were an adequate guide to adjuvant treatment.

Axillary dissection after neoadjuvant treatment in patients downstaging to cN0

When SNB was first used to stage the axilla, it was controversial whether it should be performed in women scheduled for neoadjuvant treatment. It was thought that the chemotherapy would alter lymphatic drainage resulting in a false negative sentinel node in an unacceptably high proportion of cases. By 2014, however the ASCO guidelines reported 'intermediate level evidence' (based on a systematic review of selected studies) that the benefits of SNB after neoadjuvant treatment outweighed the harms [13]. Nevertheless the guidelines did not recommend SNB in women with a metastatic axilla prior to chemotherapy, even if it became cN0 afterwards. The reason given was that the false negative rate (FNR) 'may range from 10% to 30%' and this was considered unacceptable.

In fact several studies have reported high FNR for SNB after neoadjuvant treatment. For example, in the four-arm SENTINA study [31], for arm C – consisting of cN1 women who became cN0

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after chemotherapy and received SNB followed by AD – the FNR was 14.2%. Similarly, in the large multicentric Z1071 trial [32], which enrolled patients with cN1 disease scheduled for neoadjuvant chemotherapy, the FNR was 12.6%. It is noteworthy, however, that other studies have not reported high FNRs for SNB after systemic neoadjuvant treatment [33–35]. Newman et al. [34] assessed 54 patients with a positive axilla confirmed by needle cytology: all received neoadjuvant chemotherapy and then underwent SNB followed by AD. The SN identification rate was 98%, while none of the 17 cases (32%) with a negative SN had residual disease in the axilla. Similarly, Canavese et al. [35] examined 64 patients with a clinically positive SN prior to neoadjuvant chemotherapy. They performed SNB followed by AD and found not only a high SN identification rate (93.8%), but also that 23 (38%) SNs were negative, only 2 of which had metastases in other non-sentinel nodes (FNR 8.7%).

Thus, from the available data, the FNR of SNB is not always 'unacceptably' high in patients who are cN1/2 prior to chemotherapy and obtain complete axillary response on clinical and imaging evaluation. Furthermore, the clinical significance a high FNR is unclear since the early randomized trials on SNB found that, while the FNR was of the order of 10% in AD arms, the axillary failure rate in SNB-only arms was of the order of 1% [7,11].

A third [36] or more [37] of node-positive patients become cN0 after neoadjuvant treatment and would benefit if AD – and the morbidity associated with it – could be safely avoided.

This issue was addressed by a retrospective single-institute study on outcomes in 396 patients after a median 61 months (interquartile range 38–82 month) of follow-up [38]. Patients were either cN0 or cN1/2 prior to neoadjuvant treatment and became or remained cN0 afterwards. They received SNB with no AD if sentinel nodes were negative. The study assessed axillary failure rates, particularly in patients who did not receive AD because the SN was negative, and also distant disease-free, overall, and disease-free survival. Axillary failure occurred in only 1 (0.7%) initially cN1/2 patient who became cN0. Five-year distant disease-free survival was 81.1% in initially cN0 and 73.4% in initially cN1/2 ($p = 0.33$) patients. Five-year overall survival was 93.3% in initially cN0 and 86.3% in initially cN1/2 ($p = 0.12$) patients. These findings suggest that SNB is acceptable in cN1/2 patients who become cN0 after neoadjuvant therapy. The authors commented that a supposed high FNR should not be used a priori to decide that initially cN1/2 patients should not receive SNB if they become cN0 following neoadjuvant treatment.

At the 2015 San Gallen consensus meeting, 90% of the panel considered that SNB was appropriate if a clinically node positive patient was downstaged to cN0 after neoadjuvant chemotherapy [23].

SNB when cancer is small and axilla is negative on ultrasound

In view of the Z0011 [24] finding that further axillary treatment is unnecessary in patients with early breast cancer and limited sentinel involvement (provided they receive whole breast irradiation and systemic therapy) the question arises as to whether SNB itself necessary in such patients. The ongoing SOUND trial is designed to answer this question [39]. SOUND is a randomised multicentric trial to compare the SNB policy (with AD if the sentinel node is macrometastatic, but not if micrometastases or ITCs only are present) with no axillary treatment in patients with small breast cancer and negative axilla on preoperative clinical examination and ultrasound. If a patient has a single doubtful node on axillary ultrasound she is still eligible if the needle biopsy is negative. Specific aims are: (a) to determine whether it is safe to avoid SNB (in fact all surgical treatment of the axilla) when preoperative examination indicates the axilla is disease free; and (b) to determine whether, after preoperative examination of the axilla indicates no axillary disease, adjuvant treatment can be chosen adequately based on the biologic characteristics of the primary, i.e. without the prognostic information obtained by SNB. The primary endpoint is distant disease-free survival. Axillary disease-free survival, and quality of life are among the secondary endpoints. The required sample size is 1560 patients. As of November 2015, over 950 patients had been recruited, and accrual completion is expected no later than 2017 [40].

Concluding remarks

The trend to reducing surgical treatment of the axilla in breast cancer patients continues. It is now established that AD is overtreatment in an important subset of patients with early breast cancer [19,24]. And there is evidence that this concept is being applied to clinical practice [26–28]. As regards application of the SNB policy (with no further axillary treatment if the sentinel nodes are negative) to patients who become cN0 after neoadjuvant treatment, this is occurring in some centres, but further data are required to corroborate existing evidence [38] that it is a safe procedure.

Ultimately the aim is to entirely eliminate surgical approaches to the axilla. Although previous studies have shown that eliminating AD has no effect on survival outcomes [41,42], axillary surgery, mainly in the form of SNB, has continued because the prognostic information that SNB provides has been considered essential for guiding adjuvant treatment. Several studies indicate that SNB status no longer has any influence on subsequent treatment decisions [30], because the information provided by immunohistochemical subtyping, clinical features, and gross pathology is more than sufficient. It is noteworthy that a secondary aim of the SOUND trial is to assess whether adjuvant treatment can be adequately based on the biologic characteristics of the primary, without the prognostic information provided by SNB [39].

Following the affirmation of SNB, preoperative imaging (mainly ultrasound, often with imaging-guided sampling) became the norm if the axilla was palpably unremarkable. Imaging findings help reduce the FNR of SNB and eliminate the need for SNB if metastatic disease is present, allowing patients to proceed directly to AD [43]. However if surgical staging of the axilla proves unnecessary, what is the role of preoperative axillary imaging? It may be useful for identifying patients with major but non-palpable axillary involvement, who would presumably be candidates for AD, although this would be anomalous since patients with limited axillary involvement on SNB would no longer be candidates for AD: for such patients preoperative axillary imaging would seem to be overexploration [43,44].

It is paradoxical, however, that while we are successfully reducing surgical treatment of the axilla, in other respects we increasing the treatment burden on breast cancer patients. Thus, current guidelines [23] recommend cytotoxic chemotherapy for most subtypes (HER2-positive luminal B-like; HER2 positive, and triple negative); and although hormone therapy alone is sufficient for luminal B and luminal A subtypes that are HER2-negative, chemotherapy is recommended for both if other factors are unfavourable. This problem is being addressed by the use of cancer gene expression profiling which may be able to identify patients who will and will not benefit from chemotherapy [45,46]. Preliminary data on the MINDACT trial, presented at the American Association for Cancer Research Annual Meeting, in April 2016, indicated that the 70-gene assay MammaPrint can identify patients with early breast cancer who can safely skip adjuvant chemotherapy, even if they have clinical characteristics suggesting they are at high risk [47]. However these tests are expensive and are unlikely to be available in less

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developed regions of the world where most breast cancers and breast cancer deaths now occur [48].

Conflict of interest statement

None declared.

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