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Treatment of the axilla in patients with primary breast cancer and low burden axillary disease: Limitations of the evidence from randomised controlled trials

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Contents

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ABSTRACT

Invasive breast cancer is the second most common cancer worldwide. It is known to metastasise to the regional axillary lymph nodes but there has been debate over what is the best way to stage and treat the axilla in patients presenting with primary breast cancer. Multiple trials over the last two decades have led to a change in practice from routine axillary lymph node dissection to sentinel lymph node biopsy in patients who are clinically lymph node negative preoperatively. This has resulted in new questions regarding subsequent treatment of some patients. This review will critically appraise the evidence on axillary treatment in patients with low burden axillary disease and highlight limitations of relevant randomised controlled trials.

1. Introduction

Breast cancer is the second most common cancer worldwide with an estimated 1.6 million new diagnoses worldwide in 2012

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(Cancer Research UK, 2015). Traditional surgical treatment of invasive breast cancer involved axillary lymph node dissection (ALND), which served as both a regional staging procedure and regional treatment. The widespread adoption of sentinel lymph node biopsy (SLNB), led to debate about the ongoing need for ALND, particularly in patients with low burden axillary disease.

Routine SNLB has replaced routine axillary lymph node dissection in patients with clinically negative axillary nodes preoperatively, but this has left interesting questions as to how to treat patients afterwards. The results of the American College of Surgeons Oncology Group Z0011 trial in women who underwent breast conserving surgery (BCS) plus whole breast irradiation (WBI) suggested that axillary treatment was potentially over-treating patients (Giuliano and Hunt, 2011). However questions have been raised as to the robustness of the methodology and results of the Z0011 trial. This article will review the Z0011 trial against the background of the most influential papers containing other RCT evidence regarding axillary treatment in primary breast cancer. In doing so, it will address five questions:

1. Is there a need for ALND in SLN negative patients
2. Is there a need for ALND in patients with a SLN micrometastasis?
3. Is there a need for ALND in patients with SLN macrometastasis?
4. Is axillary radiotherapy equivalent to ALND in patients with a SLN macrometastasis?
5. In women with node positive or high risk node negative breast cancer who have undergone BCS + WBI (+ ALND if node positive), does the addition of regional nodal irradiation (RNI) to WBI improve outcome, where all patients were treated with adjuvant systemic therapy?

2. Question 1: Is there a need for axillary lymph node dissection in sentinel lymph node negative patients. (NSABP B32 trial, ClinicalTrials.gov NCT 00003830)

The theoretical risk of SLNB compared to ALND is that SLNB alone could miss regional lymph node metastases to the axilla and hence under stage the disease. This would result in 'under-treatment' of the axilla with negative impact on long term survival. NSABP B32 (Krag et al., 2010) was a trial carried out to address these concerns. This large, multicentre randomized controlled trial recruited 5611 patients with invasive breast cancer and randomized them to two groups which were well matched for patient demographic and tumour biology criteria. Group 1 had underwent routine ALND after the sentinel node was sampled no matter the result, whilst Group 2 only underwent ALND if the sentinel node was positive.

Overall there were 3986 patients who were lymph node negative on SLNB. Of these, 2011 were in Group 1 and went on to have ALND and 1975 were in Group 2 who had no further axillary surgery. There was no difference in overall survival (the primary endpoint), disease free survival (DFS) or regional control between the two groups. Morbidity was significantly lower in the SNLB only group. It should be noted that while the Log-rank comparison of overall survival in Groups 1 and 2 showed no evidence of a difference (p = 0·12), the analysis yielded an unadjusted hazard ratio of 1·20 (95% CI 0·96–1·50) – i.e. 20% difference in overall survival in favour of the ALND which was statistically non-significant. The overall survival for both groups was 91·8% (95% CI 90·4–93·3) in group 1 and 90·3% (88·8–91·8) giving an absolute difference in OS of 1.5% It should also be noted that in this trial, the false negative rate following SLNB was 9.8% (95% CI 7.8-12.2) with an overall success rate of 97.2% (95% CI 96.4-97.7) (Krag et al., 2007). Despite around 10% of patients in the SLNB only group being lymph node positive, the study met its non-inferiority endpoint. At the same time it could be argued that the non-significant increase of 20% all cause mortality in patients treated by SLNB alone may have been linked to ~10% of these patients having positive nodes (based on staging data from the ALND arm of the study).

After longer follow-up, the overall survival at 10 yrs, published in an abstract of a meeting presentation, reported that there continued to be no significant difference in OS between the two groups (HR: 1.11, p = 0.27). 10 yr Kaplan-Meier (K-M) estimates for OS are 87.8% for SNR alone and 88.9% for SNR + AD – ie an absolute difference of 1.1% (Julian et al., 2013).

In summary, NSABP B32 provides good level 1 evidence, from a large, appropriately powered phase 3 RCT that SLNB is a reliable technique for staging the axilla and routine axillary clearance does not provide a survival benefit to SNLB node negative patients.

3. Question 2: Is there a need for ALND in patients with a SLN micrometastasis? (IBCSG 23-01 trial, ClinicalTrials.gov NCT00072293)

Since the adoption of SNLB, controversy has surrounded the management of patients who have a micrometastasis (≤2 mm). IBCSG 23-01 (Galimberti et al., 2013) randomised 931 patients with micrometastasis on SNLB to either undergo ALND or no local treatment to the axilla in a 1:1 ratio. This was a multicentre, randomised, non-blinded, non-inferiority, phase 3 trial, in which patients were eligible if they had clinically non-palpable axillary lymph node(s) and a primary tumour of 5 cm or less and who, after SLNB, had one or more micro-metastatic (≤2 mm) sentinel lymph nodes with no extracapsular extension. The primary endpoint was disease-free survival. Non-inferiority was defined as a hazard ratio (HR) of less than 1·25 for no axillary dissection versus axillary dissection. This means by the omission of ALND for patients with micrometastases that a survival difference of up to 25% more would be accepted as 'confirming' that SLNB was non-inferior to ALND. This is a very large margin to regard as an acceptable hazard ratio for a group of patients with only micrometastases who were otherwise receiving optimal anti-cancer care.

After the exclusion of three patients, 464 patients were in the axillary dissection group and 467 patients were in the no axillary dissection group. With a median follow-up of 5·0 (IQR 3·6–7·3) years, the study reported 69 disease-free survival events in the axillary dissection group and 55 events in the no axillary dissection group. Breast-cancer-related events were reported in 48 patients in the axillary dissection group and 47 in the no axillary dissection group (ten local recurrences in the axillary dissection group and eight in the no axillary dissection group; three and nine contralateral breast cancers; one and five regional recurrences; and 34 and 25 distant relapses). Other non-breast cancer events were recorded in 21 patients in the axillary dissection group and eight in the no axillary dissection group (20 and six second non-breast malignancies; and one and two deaths not due to a cancer event respectively). The difference in the total number of disease free events between the two groups (i.e. 69 versus 55) is explicable by the n = 14 difference in non-breast cancer malignancies between the two groups (i.e. 20 versus 6) which is likely a chance event.

This trial showed no difference in disease free survival, overall survival or recurrence. The 5-year disease-free survival, the primary endpoint, was 87·8% (95% CI 84·4–91·2) in the group without axillary dissection and 84·4% (80·7–88·1) in the group with axillary dissection (log-rank p = 0·16) The HR for no axillary dissection vs axillary dissection was 0·78, 95% CI 0·55–1·11, non-inferiority p = 0·0042, in favour of no axillary dissection). This improvement in the HR in favour of the group omitted ALND, which is surprising, is explicable by the difference in non-breast cancer malignancies (n = 14)