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Opinion

Axilla Management Trials in Breast Cancer-A Requiem for Clinical Equipoise

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Opinion

Once upon a time, long ago, the National Adjuvant Breast and Bowel Project (NSABP) team asked two questions: (i) whether in patients with clinically negative nodes, total mastectomy with subsequent as needed axillary dissection is as effective as radical mastectomy, and whether, total mastectomy with subsequent as needed axillary dissection is as effective as total mastectomy plus postoperative regional radiation, and (ii) whether in patients with clinically node positive disease, total mastectomy plus postoperative regional radiation is equivalent to radical mastectomy. In 1971, the B-04 trial was born! The short-term outcome was reported in 1977; key findings were that there were no significant differences in locoregional failures, distant failures, or overall survival among treatment groups for both node negative and node positive patients [1]. However, 18.6% of patients with clinically node negative disease underwent subsequent axillary dissections during follow up. As the trial was concluding, the role of systemic therapy was being developed utilizing a pathologically positive node as a marker of high-risk disease eligible for adjuvant systemic chemotherapy. Therefore, axillary dissection became the standard of care for next two decades for both clinically node negative and node positive disease, so that 19% of clinical node negative patients could avoid a second operation, and pathology form the nodes could inform adjuvant therapy decisions. A 25-year follow up of NSABP-04 trial reconfirmed that treatment of axilla has no bearing on survival [2]. The criticism of B-04 trial has been that up to 10 nodes were removed incidentally in 33% of total mastectomy alone group and that the trial was not powered to detect small differences in survival. Subsequent trials and metanalyses concluded that axillary dissection conferred no survival benefit in early-stage node negative breast cancer [3]. As we entered 21st century, it was clear that pathological evaluation of axillary nodes has staging value only by virtue of informing the prognosis and adjuvant therapy decisions, albeit the procedure was associated with high morbidity in terms of lymphedema, shoulder range of motion dysfunction, and sensory deficit.

Since the question of therapeutic value of axillary surgery was settled, the goal of exploring less invasive axillary staging options, such as sentinel node biopsy, should have focused on trial designs to document accuracy of staging and rate of complications. If we take a position that accurate axillary staging is important, then we should not continue to de-escalate axillary surgery based on B-04 outcome in favor of a procedure that is inaccurate just because it has lower complication rate. On the contrary, if accurate pathological staging is not clinically important, then we should abandon any axillary surgery because the complication rate will be zero for no axillary surgery. In the era of personalized medicine and therapeutic decisions based on molecular profiling of the primary tumor, the latter argument is plausible. First, the NSABP B-32 trial asked the question if sentinel node biopsy alone, in clinical node negative patients (and pathological negative sentinel node) would be non-inferior to axillary dissection in terms of survival and regional control [4]-a question already answered by B-04 [1, 2]. Indeed, morbidity and false negative rate were measured and reported; the false negative rate being 9.8%. Despite the goal of false negative rate of <5% for sentinel node biopsy set forth by the American Society of Clinical Oncology before abandoning axillary

dissection, B-32 trial changed practice and axillary dissection was abandoned because the morbidity of sentinel node biopsy is much lower than axillary dissection [4] and survival is comparable. So, now we perform a relatively inaccurate staging procedure with 8% rate of lymphedema, when we can be relatively inaccurate with clinical and non-invasive staging, with no complications if we abandon axillary procedure without inferior survival. If accurate staging is important than we must consider B-32 as a negative trial, particularly when only one sentinel node is identified which was associated with an 18% false negative rate [5] (mean number of sentinel nodes in B-32 trial was 1.3). It seems that we designed the trial as if the question of non-inferiority was not settled and it was never about staging-no clinical equipoise! Then we re-confirmed the same non-inferiority in American College of Surgeons Oncology Group (ACOSOG) Z0011 trial [6].

The next step was to document if sentinel node biopsy is accurate in clinically node positive patients that experience complete axillary response to neoadjuvant chemotherapy; ACOSOG Z1071 trial was born [7]! The threshold for rejecting the sentinel biopsy was set at 10% and the actual false negative rate was 12.6% -another negative trial. Once again, subgroup analyses and importance of number of sentinel node was highlighted to improve the false negative rate and practice of utilizing post neoadjuvant sentinel node biopsy for staging was largely adopted. In addition, the question to abandon axillary dissection in non-responding nodal disease after neoadjuvant chemotherapy was already raised and trial design to randomize post neoadjuvant pathological node positive patients to completion axillary dissection or not was submitted before the results of Z1071 were reported (NCT01901094; Alliance A011202) [8]. Do these trials represent a position of clinical equipoise? At this point, we have not seen the results of A011202 trial, and many surgeons have already omitted axillary dissection despite residual axillary disease [9, 10]. Whereas B-04 trial did show equivalent survival outcome for node positive disease whether patients received regional radiation or axillary dissection; those data are not entirely applicable to documented residual disease exhibiting resistance to first line systemic therapy.

On careful analysis, it is easy to determine that the trials discussed above have shown that sentinel node biopsy is an accurate staging technique in patients who are least likely to benefit from staging (T1 tumors) and not accurate in patients whose adjuvant treatment are most likely to be impacted by node positive disease (T3 tumors and post neoadjuvant chemotherapy, particularly, tumor biology least likely to respond) [11]. It seems that when we have an a priori bias to abandon axillary dissection, we choose to rely on B-04 data, despite a negative trial on accuracy of sentinel node biopsy. The contention is not that B-04 data are not valuable; it is that the scientific community needs to reach a consensus regarding the following:

1. Do we accept the results of B-04 trial despite the original criticism regarding power to detect small differences in survival?

If the answer is yes, then we know that:

- there is no therapeutic advantage to axillary surgery.

- Axillary dissection is the gold standard for axillary staging.

- Axillary dissection is associated with higher morbidity.

Given these facts, the only logical explanation for axillary dissection remaining the standard of care following B-04 is that the importance of accurate axillary staging was deemed paramount.

Therefore,

2. Should the role of sentinel node biopsy evaluation focus on accuracy and morbidity only?

If yes, then we know that:

- Sentinel node biopsy is not accurate in clinical scenarios where it is most important.

- Morbidity of sentinel node biopsy is much less than axillary dissection but not negligible.

Continuing to interrogate the role of sentinel node biopsy is just confirming that we are compromising accuracy of axillary staging in favor of less morbidity. If we decide that morbidity trumps staging, which may be reasonable in certain circumstances, then zero morbidity is better than less morbidity. Accepting negative studies on sentinel node biopsy in breast cancer as practice changing because of the comfort zone derived from B-04 trial does not represent the basic tenant of clinical equipoise [12]. Finally, money not only talks but it screams with the current burden of health care costs; the average cost of National Cancer Institute Sponsored Clinical Trial Network reports the average cost of clinical trial to be $7.5 million, and the average cost of practice influential trial to be $16.6 million [13]. We must choose wisely!

Conflict of Interest

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Ethical Approval

Not required.

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