Optimal management of sentinel lymph node positive biopsy patients in early breast cancer

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What is the optimal management of a positive sentinel lymph node (SLN) in patients with early stage breast cancer? Prior to the widespread adoption of SLN biopsy, axillary lymph node dissection (ALND) was considered to have both therapeutic and prognostic benefit. Multiple studies have shown the accuracy and predictive value of the SLN procedure (1) and randomized trials confirmed that patients with negative SLN could forgo ALND (2,3).

For patients with a positive SLN, a completion ALND was considered beneficial for optimizing regional control and for potentially improving survival. Yet some retrospective studies showed low axillary recurrence in women with positive SLN who did not have an ALND (4).

In the past decade several randomized studies have addressed whether ALND is indicated following a positive SLN biopsy in patients with early breast cancer and clinically negative lymph nodes (LNs). Other therapeutic modalities, including systemic therapy and radiation, may contribute to regional control. In addition, clinical and biologic markers are widely used as prognostic indicators.

EORTC 10981-2203, the AMAROS trial, was initiated in 2001 to assess whether patients with a positive SLN could be treated with radiotherapy instead of ALND, with comparable medical benefit and fewer side effects (5). Eligible patients with invasive breast cancers measuring ≤3 cm and clinically negative LNs were randomized to ALND or axillary radiation following a positive SLN biopsy. Local treatment included mastectomy or breast conservation surgery. ALND included anatomical levels I and II to include at least 10 LNs. Axillary radiotherapy included all three axillary levels and the medial supraclavicular fossa. The prescribed dose was 50 Gy in 25 fractions of 2 Gy per fraction. Additional metastatic LNs were found in 33% of patients undergoing ALND.

With a median follow up of 6.1 years, there was no statistically significant difference in axillary recurrence, disease free survival (DFS) or overall survival between the two groups. Five-year axillary recurrence was 0.43% after ALND *vs.* 1.19% after axillary radiotherapy. Lymphedema was significantly greater in the ALND group. The AMAROS trial showed that ALND and axillary radiotherapy provided comparable axillary control in the study population with significantly less morbidity in the radiotherapy group.

The AMAROS trial was the first study to prospectively compare axillary radiation therapy (RT) against ALND in early stage breast cancer patients with positive SLN. Its value lies in demonstrating low axillary recurrence following radiation, alongside with decreased morbidity compared to ALND. The results of this trial should be viewed in the context of historic data on risks of clinical axillary recurrence, other recent trials addressing positive SLND, and contemporary breast cancer management.

In the NSABP B-04 (6) trial about 40% of patients with clinically negative nodes treated by radical mastectomy were found to have positive LNs. Patients treated with total mastectomy (no ALND) without axillary radiation were followed. Only about half of these women developed a clinically positive axillary node as a first event. The data from NSABP B-04 suggests that leaving positive nodes unresected did not significantly increase the rate of distant recurrence or breast cancer specific mortality. At 25 years of follow up there was no survival advantage from RT after total mastectomy in women with clinically negative nodes.

A French trial, initiated before the introduction of SLN biopsy, randomized patients with breast cancer <3 cm and clinically negative LNs to ALND or axillary radiotherapy (7). 21% of the ALND patients had positive LNs. At 15 years follow up there was no difference in long-term survival between the two groups. There was a small difference in axillary LN recurrence 1% in the ALND group *vs.* 3% in the RT group.

The American College of Surgeons Oncology Group Z0011 study (8) was a prospective trial, which evaluated survival of patients with clinically negative LNs randomized to an ALND *vs.* no further treatment after a positive SLN biopsy. Patients were treated with breast conserving surgery, lumpectomy followed by radiation. All patients received opposed tangential field whole breast radiation; third field radiation to the regional nodes was not permitted. Of patients undergoing an ALND, 27.3% had an additional positive lymph node. At 6.3 years follow up there was no difference in local or regional recurrence between the two groups. The use of SLND alone did not result in inferior survival.

IBCSG-2301, a multi-center, randomized phase 3 study of ALND *vs.* no ALND in patients with sentinel-node micro-metastases (<2 mm) concluded that axillary dissection could be avoided in patients with early breast cancer and limited sentinel LN involvement (9).

The AMAROS results suggest that radiation provides equivalent outcomes to SLN positive patients as ALND with less morbidity. The ACOG Z011 study demonstrates comparable outcomes with standard whole breast radiation, without the addition of regional node irradiation. Discussants of the ACOG Z011 trial suggest that standard opposed tangential fields irradiate the SLND site, much of the level I axilla and a portion of the level II axilla. The reference cited, published in 2001 (10) is based on two dimensional imaging and planning, with clips used as surrogates for inclusion of axillary contents. A more recent review of axillary lymph node coverage in standard tangential fields based on CT-based 3D planning shows that only about 55% of level I-II axillary LNs are covered by 95% of the prescribed dose (11). Despite the lack of complete axillary coverage by the radiation field, the axillary recurrence rate in the Z011 trial was extremely low, less than 2%. The additional therapeutic benefit of treating the entire axillary lymph node volumes as described in the AMAROS study is likely to be minimal. The larger field would increase the volume of normal tissue irradiated and potentially the morbidity and cost of treatment.

Progress in locoregional therapy for early stage breast cancer has resulted in decreasing the morbidity of breast cancer treatment. The NSABP B-04 trial with 25-year follow-up data demonstrated equivalent overall survival between radical mastectomy, mastectomy with radiation, and mastectomy alone in clinically node-negative women (6). Subsequently, the SLN biopsy procedure has been established as the staging procedure of choice for women with early-stage, node-negative breast cancer, allowing for accurate staging of the axilla while decreasing the rates of lymphedema, arm dysfunction, and pain. There has been an effort to identity node-positive women in whom the morbidity of a completion axillary dissection may be avoided with acceptably low risk of axillary recurrence. The SLN biopsy is falsely negative in about 5% of node-positive patients (12), but this does not appear to have a corresponding axillary recurrence rate. Despite presumably untreated disease in the axilla, the axillary recurrence rate following a negative SLNB is far lower than expected based on the FNR and suggests that such disease is less likely to produce clinical disease.

Improved mortality from breast cancer can be attributed not only to increased screening but also improvements in therapy. Women in the NSABP B-04 trial did not receive systemic therapy, while in more recent trials with shorter follow-up, the majority of women [95-97% in the IBCSG 23-01 trial (9) and 96-97% in Z0011 (8)] received at least some form of adjuvant systemic therapy. The use of genomic profiling has greatly advanced direction of systemic therapy with better tailored therapy, and some women within the traditionally considered "low-risk" group (node-negative women with tumors that are hormone receptor-positive and HER2-neu-negative) have been identified as having tumors with higher risk for distant recurrence and appropriately offered systemic therapy. One such assay, the Oncotype Dx assay, has demonstrated an association between higher score and locoregional recurrence risk (13). In addition, neoadjuvant systemic therapy can effectively treat axillary nodal disease in up to 30-40% of patients (14). While the ACOSOG Z1071 trial showed an inferior false negative rate of 12.6% for SLNB following neoadjuvant chemotherapy, multiple studies nevertheless highlight the ability of systemic therapy to eradicate some disease in the axilla and may allow for alternate therapy to the axilla (15).

Recently, more women are avoiding a completion axillary dissection in the event of a positive sentinel node biopsy. This is both patient- and surgeon-driven and therefore represents selection bias; however, these studies demonstrate

low risks of axillary recurrence following sentinel node biopsy only. Nomogram tools have been developed to assist surgeons and patients in selection of patients for completion axillary dissection, and these rely on predictors such as tumor size, tumor grade, estrogen receptor status, and lymphovascular invasion; using such nomograms has been shown to decrease the rate of completion axillary dissection in a subset of women with more favorable tumor factors with only a marginally higher rate of axillary recurrence (2% *vs.* 0.4% at 23-30 months) (16). The AMAROS trial did not evaluate hormonal status or LVI status, but the low level of axillary recurrence suggests that radiation represents an acceptable means of disease control in the axilla regardless of tumor type. While the ACOSOG Z0011 trial included only women undergoing breast conservation with adjuvant RT, both the IBCSG 23-01 and the AMAROS trial allowed patients to undergo either breast conservation or mastectomy (9% in the IBCSG trial and 17-18% in the AMAROS trial) for their local treatment. Interestingly, 19% of patients undergoing breast conservation in the IBCSG trial received intraoperative RT only, thereby missing the previously offered suggestion of axillary treatment with standard tangential fields. This may also represent the efficacy of systemic treatment in eradication of axillary disease.

While there is little, if any, controversy to the prognostic value of axillary LNs, not everyone is in agreement to the therapeutic benefit of axillary nodal dissection. The impact of axillary nodal dissection on survival is not well established. Most of the data showing improved survival are derived from either retrospective studies, or from studies that justifiably allowed adjuvant chemotherapy for patients post-dissection if they were found to have positive nodes. Adjuvant chemotherapy is expected to positively impact survival, which can lead to a biased improved survival in patients undergoing ALND compared to those who did not (7,17,18). On the other hand, the NSABP B04 has demonstrated no improvement in survival with removal of occult axillary metastases (8). In addition, a meta-analysis of three large trials comparing axillary dissection *vs.* no dissection, found no improvement in overall survival, axillary recurrence or ipsilateral breast recurrence in axillary dissection groups (19).

The National Comprehensive Cancer Network (NCCN) has taken an early step toward reducing the number of axillary dissections for clinically negative axilla (version 3.2014). Patients with clinically negative axilla, who underwent lumpectomy and received no neoadjuvant chemotherapy, and were found to have less than three positive sentinel nodes and T1 or T2 tumor, have the option of forgoing completion axillary dissection, given that they will be proceeding with adjuvant radiotherapy.

In order to address this debate, a prospective and well-powered trial that places the benefits and adverse events on two arms of a scale is needed. Management of axillary nodes has been evolving in a logical, albeit slow, pattern; that is, towards minimizing long term complications, without compromising outcome.

In this regard, the AMAROS trial represents a landmark article that may potentially impact standard of care practices. Needless to say that longer follow up is needed for more robust conclusions.

Nevertheless, there still remain several inevitable questions that need to be addressed. First, can we forgo ASLN procedure in patients who have clinically node negative axilla? What about the infrequent patient that is found to have three or more positive sentinel nodes? And finally, can neoadjuvant systemic therapy eliminate the need for axillary dissection for clinically node positive patients who has good response. This is what the ongoing NSABP-B51/RTOG-1304 is designed to address (20).

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