Analysis of Axillary Management Following Mastectomy With a Positive Sentinel Lymph Node Biopsy

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Abstract

**BACKGROUND**: Axillary lymph node dissection (ALND) with or without postmastectomy radiation therapy (PMRT) was traditionally the standard of care for patients with a positive sentinel node following mastectomy. However, recent clinical trial data has led to an interest in de-escalating therapy and a debate over optimal axillary management. We sought to assess current practice patterns and the impact of different approaches to managing positive sentinel nodes following mastectomy.

**METHODS**: Using the National Cancer Database (NCDB), patients with clinical T1-2 N0 M0 breast cancer from 2012-2015 treated with a mastectomy who were found to have a single positive sentinel node were analyzed. A logistic regression model stratified by patients’ characteristics in association to the type of axillary treatment received was performed.

**RESULTS**: We identified 12,137 women with a positive sentinel lymph node biopsy (SLNB) at the time of mastectomy. Of these, 4,221 had an ALND; 1,609 received PMRT; 1,565 underwent combination therapy, and 4,742 had no further treatment following SLNB (NFT). Factors associated with an increased likelihood of further axillary treatment included younger age (<40), Midwest location, larger primary tumor size (T2), and high grade. There was no difference in short-term overall survival among these approaches.

**CONCLUSION**: Our study indicates significant practice variation in the axillary management of patients with metastasis limited to a single sentinel node undergoing mastectomy. The clinical variation observed raises the possibility of unnecessary or overtreatment of the axilla. These findings suggest a need to expand the adoption of evidenced-based clinical protocols to improve quality of care.

Synopsis

Significant clinical practice variation in axillary management was observed in patients with clinically T1-2, cN0 breast cancer who had minimal sentinel nodal disease.

Introduction:

Axillary lymph node dissection (ALND) has traditionally been the standard of care for patients with breast cancer undergoing mastectomy who are found to have a positive sentinel node. ALND is associated with potentially significant morbidity, including the development of lymphedema, impairment of shoulder mobility, neuralgia, and seroma.\(^1\)\(^-\)\(^4\) As the surgical paradigm has shifted in favor of less invasive procedures to reduce morbidity and improve quality-of-life among patients with breast cancer, the contemporary management of axillary lymph nodes is a topic of debate.\(^5\)

In particular, the management of nodal disease in patients with a clinically negative axillary exam undergoing a mastectomy is in evolution. The American College of Surgeons Oncology Group (ACOSOG) Z0011 trial demonstrated the lack of an associated survival benefit from completion axillary lymph node
dissection in selected patients with limited nodal involvement. However, this study only included patients undergoing breast conservation; therefore, the results cannot simply be extrapolated and applied to patients undergoing mastectomy.

The European Organization for Research and Treatment of Cancer (EORTC) AMAROS trial showed that axillary radiation therapy without ALND for the management of positive sentinel nodes provides adequate regional control in patients with early-stage breast cancer. However, patients receiving a mastectomy were under-represented in this study. More evidence is needed to guide clinical management decisions for patients with sentinel node metastasis who have undergone a mastectomy.

Our objective in this study is to evaluate current practice patterns regarding different approaches to axillary management in clinically node-negative patients undergoing a mastectomy who subsequently have limited disease burden identified on SLN biopsy. Specifically, we assess the utilization of ALND alone, post-mastectomy radiation therapy (PMRT) alone, combined ALND and PMRT (combination therapy), or no further treatment following sentinel lymph node biopsy (NFT).

Examining clinical practice variation is an important step in understanding the effectiveness of care delivery and identifying discrepancies that could indicate overtreatment or undertreatment. By evaluating clinical practice patterns, we seek to determine if there are variations in axillary management that may indicate the need for evidence-based standardization of practice.

**Methods:**

**Data Source**

We queried The National Cancer Database (NCDB), a joint effort of the American College of Surgeons and the American Cancer Society. The NCDB is a de-identified hospital-based registry database that captures more than 70% of all newly diagnosed cancers in the United States. The institutional review board deemed this an exempt study.

**Patients**

We retrospectively identified patients from the NCDB with clinical T1-2, primary invasive breast cancer diagnosed and treated with mastectomy from 2012–2015 who were clinically node-negative but found to have a positive sentinel node metastasis at the time of definitive surgery. Sentinel lymph node involvement was categorized into three groups: isolated tumor cells (ITC), micro-metastasis, and macro-metastasis involving a single node. Patients who underwent neoadjuvant chemotherapy or received radiation intraoperatively or before surgery were excluded.

We collected demographic characteristics and clinical and pathologic data, including age, gender, ethnicity, insurance, income, and comorbidity score (using the Deyo modification of the Charlson index). Facility location was categorized as metro or other, and institutions were classified as academic or
community medical centers. Each facility’s surgical volume was defined by tertile, grouped into low-, medium, and high-volume facilities.

Patients were subsequently categorized into four groups based on axillary treatment strategies: ALND alone, PMRT alone, combined ALND + PMRT (combination therapy), or no further treatment following sentinel node biopsy (NFT). The primary outcome of interest was identifying clinical practice patterns and specific factors influencing treatment approaches for axillary management. Short-term overall survival was a secondary outcome evaluated.

**Statistical Analysis**

Descriptive statistics were used to summarize the study cohort according to demographic data, tumor characteristics, and treatment modality. Chi-square test was used to test differences of categorical variables, and Kruskal-Wallis tests were used to detect differences for continuous variables between groups. A multinomial logistic regression model was fit to determine the association between baseline characteristics (demographics, disease characteristics, and characteristics of the treatment center), nodal involvement (i.e., ITC, micro-metastasis, or macro-metastasis limited to a single node), and the different treatment modalities.

Survival analysis was performed for patients with limited nodal involvement (i.e., ITC, micro-metastasis, or macro-metastasis limited to a single node) and was limited to patients with follow-up data. A Cox proportional hazards regression model was used to estimate hazard ratios for the different treatment groups. All statistical analyses were performed with SAS 9.4 (SAS Institute, Cary, NC, USA)

**Results**

Our study identified 12,137 women with a single positive SLNB at the time of mastectomy between the years 2012 and 2015. Of these, 4,221 (35%) proceeded to have an ALND; 1,609 (13%) received PMRT alone; 1,565 (13%) underwent combination therapy; and 4,742 (39%) had NFT (Figure 1). Cohort characteristics are summarized in Table 1.

On the univariable analysis, a decreasing trend in the rate of receiving an ALND was evidenced throughout our study time frame. In 2012, 1,045 (39.2%) of the patients received an ALND for their axillary management, while in 2015, only 956 (31%) received an ALND. In contrast, the percentage of patients receiving PMRT increased over the study period. In 2012 there were 278 (10.4%) patients undergoing PMRT alone, compared to 495 (16%) in 2015. These trends persisted on multivariable analysis, where the odds of receiving a PMRT were 1.47 (95%CI 1.23-1.75) higher in 2015 compared to 2012. The decrease in ALND was also significant, with an OR of 0.74 (95%CI 0.65-0.84) in 2015 compared to 2012.

Specific clinical factors were associated with axillary management trends. Patients with larger tumor size (T2 vs. T1) more often received axillary treatment, PMRT (OR 1.67; CI 1.49-1.87), ALND (OR 1.23; CI 1.13-1.35), or combination therapy (OR 1.88; CI 1.70-2.07). High tumor grade was associated with a higher
probability of receiving PMRT (OR 1.16; CI 1.01-1.34), ALND (OR 1.14; CI 1.02-1.27), or combination therapy (OR 1.29; CI 1.15-1.45) compared to intermediate grade.

The probability of treatment beyond SLNB was inversely associated with age, where patients under 40 had a higher probability of receiving PMRT (OR 1.37; CI 1.09-1.72) or combination therapy (OR 1.77; CI 1.46-2.16) as compared to the reference age group of 40-54.

Facilities located in the Northeast and Midwest were associated with an increased probability of performing PMRT (OR 1.24; CI 1.03-1.49) (OR 1.19:CI 1.01-1.39), respectively, as well as combination therapy (OR1.22; CI 1.05-1.42) (OR 1.40; CI 1.23-1.59), respectively, compared to facilities located in the South (Table 2).

Nodal involvement limited to ITCs was associated with a lower probability of receiving PMRT (OR 0.11; CI 0.09-0.13), ALND (OR 0.11; CI 0.10-0.12), or combination therapy (OR 0.02; CI 0.02-0.03) as compared to macrometastasis. Similarly, involvement limited to micrometastasis was associated with a lower probability of receiving PMRT (OR 0.34; CI 0.30-0.39), ALND (OR 0.25; CI 0.23-0.28), or combination therapy (OR 0.10; CI 0.08-0.11) compared to macrometastasis.

Finally, low-volume facilities were associated with less probability of performing an ALND (OR 0.67; CI 0.55-0.81) or combination therapy (OR 0.62; CI 0.50-0.78) compared to high-volume facilities (Table 2).

When performing an undadjusted survival analysis between the different treatment modalities, no survival difference was identified between NFT, ALND, PMRT, or combination therapy in patients with metastasis limited to one sentinel node, log-rank p-value = 0.062 (Figure 2). Moreover, after adjusting for multiple co-variables with a Cox proportional hazards model stratified by ITC, micrometastasis, and macrometastasis, there was no survival difference between ALND, PMRT, or combination therapy compared to NFT (Table 3). The median follow-up period for our cohort, was 32.57 months (Q1-Q3, 24.2 – 41.8 months).

Discussion

The benefit of PMRT in early breast cancer with a limited nodal disease continues to be a topic of controversy in the field of breast surgery. ALND and PMRT are treatment modalities that serve an important role in axillary management following mastectomy with nodal involvement. However, the optimal use of ALND, PMRT, or combination therapy in managing limited nodal disease following mastectomy has yet to be definitively determined. Areas of clinical uncertainty are prone to cause variation in care delivery. These variations can result in overtreatment or undertreatment of patients.

Our study demonstrated significant clinical practice variation in the axillary management of clinically node-negative patients found to have a positive SLN at the time of mastectomy. In our cohort, nearly half of all patients received no further therapy following SLNB, while the remaining patients received ALND,
PMRT, or combination therapy. Despite limited follow-up in the survival analysis, there was no difference in overall survival associated with the method of axillary management.

These discrepancies in clinical care indicate that patients may be at risk for either overtreatment or undertreatment, resulting in inconsistent clinical outcomes, costs, and morbidity. Furthermore, our findings contribute to understanding the management of a patient group that has been underrepresented in clinical trials.

The likelihood of receiving further axillary treatment was higher in patients under 40 years of age. This finding may reflect a propensity to treat younger patients more aggressively in hope of optimizing survival outcomes. However, prior clinical trials evaluating axillary management did not show any association with age and clinical outcomes.19

The type of facility (academic vs. community program) did not significantly influence trends for additional axillary treatment. However, facility volume was observed to influence axillary management decisions. Lower volume facilities were more likely to omit ALND and PMRT, treating patients with SLNB alone (i.e., NFT). This observation may reflect inherent practice differences in these facilities, or it may be due to lower volume centers referring patients to higher volume centers for additional axillary treatment.

Patients with ITCs or micrometastasis were less likely to receive additional axillary treatment with ALND or PMRT. This trend is in line with the growing recognition of the limited impact of additional axillary treatment on locoregional control or overall survival in select patients.8–10,14–18 The additional information gained from the completion node dissection, beyond what is already gathered from the sentinel node, may not always be critical in clinical decision-making.

Additionally, we observed that over time an increasing number of patients had omission of ALND. This trend may represent incremental adoption of clinical trial data, increasing comfort de-escalating therapy based on the growing body of evidence. Interestingly, this trend was observed even in patients with macrometastasis. Of note, the database assessed for the study is unable to determine if patients with a single macrometastasis treated with SLNB alone had additional negative sentinel nodes, possibly lowering the perceived risk of residual nodal involvement.

The importance of PMRT or ALND for locoregional control and perhaps even long-term survival still requires further evaluation. Treatment decisions in these scenarios are ideally made within the context of a multidisciplinary team discussion. Multiple ongoing clinical trials are evaluating if axillary treatment can be safely omitted in sentinel node-positive breast cancer patients undergoing a mastectomy. The results may lead further treatment de-escalation, resulting in lower axillary morbidity rates and improved quality of life without compromising survival outcomes.

Limitations:
The retrospective nature of our study does not control for all confounders and is potentially subject to selection bias. Since the NCDB does not differentiate between ALND and SLNB surgeries before 2012, our sample size and length of survival follow-up was limited. Moreover, the NCDB lacks dosimetric information on the field arrangement for radiotherapy and does not differentiate between chest wall with regional node irradiation and chest wall irradiation alone. The short overall survival analysis in this study is a recognized limitation owning to the recent timeframe of the clinical practice evaluated. Longer follow-up is planned in subsequent studies. Lastly, we could not evaluate local failure rates, which is an important data point in determining the benefit of PMRT and ALND in patients with positive N1 disease.

Conclusion:

Our study found significant clinical practice variation when comparing different approaches to axillary management in patients with limited sentinel node metastasis following mastectomy. Despite landmark clinical trial data, discrepancies in the patterns of care for axillary surgery are still present. A significant proportion of patients underwent axillary treatment, which may represent overtreatment of the axilla based on recent clinical trial data.

Although further delineation into these practice patterns is required, the findings suggest a need to advance the adoption of evidence-based clinical protocols to improve the quality of care. Until further prospective studies are performed, the potential benefit of additional axillary treatment for locoregional control should be determined in the context of a multidisciplinary treatment team, including engagement with the patient in a shared decision-making process.

Declarations

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**Tables**

Due to technical limitations, table 1-3 is only available as a download in the Supplemental Files section.

**Figures**
Figure 1

Study Cohort Sample Construction Flow Diagram
Figure 2

Kaplan-Meier analysis for all the treatment modalities (ITC, micro-metastasis, and macro-metastasis)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.pdf
- Table2.pdf
- Table3.pdf