



Could lymph node evaluation be eliminated in nearly 50% of women with early stage ER/PR positive breast cancer?



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ARTICLE INFO

Article history:

Received 27 March 2020

Received in revised form

16 July 2020

Accepted 4 October 2020

Keywords:

Breast cancer

Sentinel lymph node biopsy

Avoiding lymph node evaluation

Risk assessment

Decision making

ABSTRACT

Background: The Society of Surgical Oncology introduced guidance discouraging routine axillary staging in women 70 years or older with invasive, clinically node negative, hormone-receptor positive breast cancer. Due to concerns this could result in patients missing necessary treatment, researchers from the Mayo Clinic developed a rule to distinguish between those at low/high-risk of having positive nodes. The purpose of this study was to validate the Mayo Clinic rule in women of all ages.

Methods: A retrospective review was conducted on patients seen in one breast surgeon's practice from January 1, 2006 through March 1, 2018. The Mayo Clinic rule was applied, and accuracy was evaluated. **Results:** Utilizing the Mayo Clinic rule, 46.8% (n = 289) of women met low-risk criteria. Unexpected positive lymph nodes in low-risk women was 10.0% (n = 29), which was similar to the Mayo Clinic study finding (7.8%, P = 0.167).

Conclusions: These data suggest the Mayo Clinic rule is reproducible. Nearly 50% of women with hormone receptor positive breast cancer could avoid axillary staging, but about 10% will have unexpected positive lymph nodes.

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Introduction

Breast cancer is the most common newly diagnosed cancer among women in the United States. The American Cancer Society estimates that in the year 2020 there will be approximately 276,480 new diagnoses of breast cancer, and despite major advances in treatment, an estimated 42,170 women will die from breast cancer.¹ It is well known that breast cancer incidence rises with increasing age.² Invasive breast cancer incidence among women younger than 65 years is 82 per 100,000 women per year, whereas incidence in those 65 years or older is 427 per 100,000 women per year.³

Axillary staging is a routine part of the surgical treatment of breast cancer and has historically influenced which adjuvant treatment is utilized beyond surgery. Nodal status remains an established prognostic factor along with tumor biology.⁴ In 2016, however, the

Society of Surgical Oncology (SSO) introduced a new guideline as part of its “Choosing Wisely Campaign” that recommended against the routine use of sentinel lymph node (SLN) biopsy among women 70 years or older with hormone receptor positive invasive breast cancer and no signs of axillary lymph node metastases on physical examination.⁵ This guideline was based on two studies that suggested no survival advantage from axillary lymph node dissection among this patient population.^{6,7} These studies, however, analyzed data collected prior to the widespread implementation of SLN biopsy, which became the standard of treatment in the early 2000s.^{8,9}

Researchers from the Mayo Clinic were concerned that a large proportion of hormone receptor positive breast cancer patients may still benefit from the knowledge of involved lymph nodes and that this new guideline may have a detrimental effect on their outcome. For this reason, a simple more selective rule was developed that could distinguish between patients who were at low and high-risk of sentinel node positivity at the time of surgery.⁹ The Mayo Clinic rule states that women ≥ 70 who have a grade 1 tumor \leq two cm in size; as well as women ≥ 70 who have a grade 2 tumor \leq one cm in size are considered low-risk and therefore do

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not routinely require sentinel lymph node biopsy.⁹ The researchers found that 7.8% of patients who met the above low-risk criteria were found to have positive nodes.⁹

Utilization of the Mayo Clinic findings would allow patients at low-risk to avoid sentinel lymph node biopsy and patients at high-risk to have the procedure, thus utilizing a more selective approach. Our study was designed to validate this Mayo Clinic rule in women of all ages to determine if even more patients may benefit from the rule and avoid lymph node evaluation. We also evaluated whether the knowledge of nodal positivity directly affected the adjuvant treatment of these women.

Methods

Participants

A retrospective review was conducted of patients 18 years of age or older diagnosed with breast cancer and who received care from one breast cancer surgeon from January 1, 2006 through March 1, 2018. Eligible patients had clinically negative nodes (no lymphadenopathy on physical exam) and a diagnosis of invasive, hormone receptor positive breast cancer. Patients who had ductal carcinoma in situ (DCIS), metastatic cancer, or chemotherapy before surgery were excluded. This study was approved by the Institutional Review Board at Ascension Via Christi Hospitals Wichita, Inc.

Data collection

The following variables were then abstracted from the medical records for eligible patients: clinically negative nodes, hormone receptor status, type of cancer (ductal vs lobular vs mixed), ER/PR status/percentages, tumor grade, tumor size, type of surgery (lumpectomy vs mastectomy), year of treatment, lymph node status, whether adjuvant treatment was added for patients who had positive lymph nodes, rationale for adjuvant treatment, and the type of adjuvant treatment that was added.

Data analysis

Patients were stratified into two age categories (18–69, and 70 and older). Data were nominal and ordinal, therefore frequencies were calculated for descriptive statistics. Pearson’s chi-square and Fisher’s exact tests were used for comparisons among variables. A Z-test was used for comparisons between this study and the initial Mayo Clinic rule study. A $P \leq 0.05$ was considered statistically significant. Statistical analyses were computed using SPSS version 19.0 (IBM Corp., Somers, New York).

Results

Of the 1284 total charts from the breast surgeon’s office, 617 met inclusion criteria and 667 were excluded. Of the 617 patients, 404 (65.5%) were between the ages of 18–69 and 213 (34.5%) were 70 years or older. After the Mayo Clinic rule was applied to these patients, 289 were considered low-risk and 328 were considered high-risk for nodal positivity (Table 1). Of the 289 who met low-risk criteria, 29 (10.0%) were found to have positive nodes (Table 2). When the nodal positivity rate among those determined to be low-risk by the rule was stratified by age, those 70 and older had a nodal positivity rate of 7.1% (n = 8), which was similar to those younger than 70 who had a rate of 11.9% (n = 21; P = 0.180). Of the 328 who met the high-risk criteria, 118 were found to have positive nodes (36.0%) and 210 were found to have negative nodes (64.0%; Table 2).

Of the 29 women among the low-risk group with positive nodes, 20 (69.0%) had their treatment changed due to knowledge of

Table 1
Risk according to Mayo Clinic rule.

Risk Level	Total	Age (years)	
		18–69	70+
High Risk:	328 (53.2%)	228 (69.5%)	100 (30.5%)
Low Risk:	289 (46.8%)	176 (60.9%)	113 (39.1%)

positive nodes (Table 3). Most of those women whose treatment changed were diagnosed before genomic scores were used to avoid chemotherapy in women who had positive lymph nodes. Fourteen of these women were 18–69 and the remaining 6 were 70 or older. Four were given chemo and radiation due to positive nodes, 12 were given chemo due to positive nodes, and 4 were given radiation due to positive nodes. Out of the 9 women that did not have their treatment changed, 5 had a low oncotype score, 1 had a low Mammoprint score, 2 had significant medical problems and 1 was noncompliant and declined radiation when it was offered.

Of the 118 women in the high-risk group with positive nodes, 92 (78.0%) had their treatment changed due to their lymph node status (Table 4). Of these, 38 received chemotherapy, 40 received both chemotherapy and radiation therapy, and 14 received radiation alone. Our data showed that when lymph nodes were positive in women over 70, 61.4% had their treatment altered by either the addition of chemotherapy and or radiation therapy. This included all women over 70 both in the high and low-risk group. In the low-risk group only 6 out of 8 of those women had their treatment changed. We also evaluated women under age 70 and found that 82.5% of the younger women had their treatment changed due to positive lymph nodes; 48.5% by the addition of chemotherapy and 33.9% by the addition of both chemotherapy and post-mastectomy radiation.

Comments

The purpose of this study was to evaluate whether the previously published Mayo Clinic rule could identify breast cancer patients who had a low enough risk of positive lymph nodes that they could potentially avoid axillary staging. Our research showed that the low and high-risk categories did work on women of all ages. The Mayo Clinic study had a nodal positivity rate of 7.8% (n = 1245) in patients meeting low-risk criteria.⁹ Our study had a nodal positivity rate of 7.1% (n = 8) in women older than 70 and 11.9% (n = 21) for women under age 70 among those meeting low-risk criteria. The overall nodal positivity rate in those meeting low-risk criteria was 10.0% (n = 29). This was not significantly different (P = 0.167) than the Mayo Clinic data. This suggests that the Mayo Clinic rule is reproducible among women of all ages with clinically node negative, hormone receptor positive breast cancer. Nearly 50% of women in this study met the described low-risk criteria and could potentially forego axillary staging. Seven to 12% of these women, however, would have unexpected positive nodes. This rate of unexpected positive nodes may or may not be acceptable depending on whether the direct knowledge of nodal positivity alters either treatment or outcome. The acceptable rate of unexpected positive nodes may also be different in younger patients compared to significantly older patients who have a limited life-expectancy, in which case higher rates of unexpected positive nodes may be acceptable in the latter but not the former.

In 2016, the Society of Surgical Oncology released a guideline recommending against the routine use of sentinel lymph node biopsy among clinically node-negative, hormone receptor positive breast cancer patients older than age 70.⁵ Studies showing disparities in treatment and outcomes for older women raise the

Table 2
Risk category according to Mayo Clinic rule by lymph node status.

High Risk 328 (53.2%)	+ Nodes 118/328 (36.0%)		- Nodes 210/328 (64.0%)	
	Age = 18-69	Age = 70+	Age = 18-69	Age = 70+
	82/228 (36.0%)	36/100 (36.0%)	146/228 (64.0%)	64/100 (64.0%)
Low Risk 289 (46.8%)	+ Nodes 29/289 (10.0%)		- Nodes 260/289 (90.0%)	
	Age = 18-69	Age = 70+	Age = 18-69	Age = 70+
	21/176 (11.9%)	8/113 (7.1%)	155/176 (88.1%)	105/113 (92.9%)

question that eliminating surgical axillary staging may lead to even further undertreatment of this population.^{10–12} This has led to controversy in this choosing wisely recommendation. Axillary staging is still commonly completed in women over 70 with ER/PR positive tumors, and lymph node positivity continues to influence whether these women undergo chemotherapy or radiation therapy.^{13,14} Our data showed that when lymph nodes were positive in women over 70, 61.4% had their treatment altered, and in the under 70 group, 82.5% had their treatment altered. When evaluating only the data regarding women in the low-risk group with unexpected positive nodes, 20/29 women had their treatment changed directly due to the lymph node positivity. Six out of 8 of these women were in the over 70 group and 14 out of 21 were in the under 70 group. Nine out of 29 women did not have their treatment altered. Six of these patients were able to avoid chemotherapy secondary to a low genomic recurrence score.

A more selective approach to SLN biopsy in women over 70 with ER/PR positive tumors, rather than outright omission may be an option to counter the above controversy. The Mayo Clinic research sought to equip providers with a practical way of identifying patients who have low or high-risk of having positive nodes rather than outright omission. Our current study confirmed the results of the Mayo Clinic research and showed that patients over 70 identified as high-risk had a nodal positivity value of 36% (n = 36), whereas patients identified as low-risk had a nodal positivity value of only 7.1% (n = 8). Surgeons could utilize the Mayo Clinic rule to select a fairly low-risk group to avoid evaluation of sentinel nodes. These low-risk patients could benefit from lower morbidity and significant cost savings by avoiding SLN biopsy. This is in accordance with the goal of The Choosing Wisely campaign.⁵ Unexpected positive sentinel lymph nodes in the low-risk group may not matter if lymph node positivity does not alter adjuvant treatment

and does not affect outcome. The Choosing Wisely Campaign recommendation was influenced by information from the CALGB 9343 trial. This trial showed that patients over age 70 who have ER/PR positive breast cancers were able to avoid radiation by taking 5 years of Tamoxifen.¹⁵ This study accrued patients prior to 1999 and therefore before sentinel node procedures became standard of care. Axillary staging was discouraged in this trial and 36–37% of those patients did not have any axillary staging. Axillary staging had little value or impact in the women in this study. Hughes et al.⁶ did a long-term follow-up of the same data, which showed that there was a small difference in local recurrence, but no difference in overall survival, distant disease-free survival, or breast preservation rates. Specifically, in the axilla, there was a 3% higher axillary recurrence rate in the group that did not have radiation. Hughes pointed out that avoiding radiation in those patients who do not have axillary staging, would result in an approximate 3% axillary recurrence. Although the rate of axillary recurrence is low in this study, avoiding radiation could still be a potential point of contention for clinicians taking care of women over 70 when the knowledge of lymph node status is unknown.

Interestingly, avoidance of radiation is not a point of contention in women under 70 who are undergoing breast preservation, since currently these patients would all receive radiation whether their nodes are positive or negative. As for chemotherapy with positive lymph nodes, Genomic testing has shown that the avoidance of chemotherapy when lymph nodes are positive in low-risk hormone receptor positive tumors is possible.¹⁶ If lymph node positivity no longer matters in the decision-making process for adjuvant treatment, then we may be able to avoid checking lymph nodes on all patients with low-risk ER/PR positive tumors independent of their age. As clinicians become more reliant on genomic testing, avoiding lymph node evaluation may become more widespread in women of

Table 3
Low-risk positive lymph nodes treatment alterations.

Changes to treatment plan based on lymph node status	Did lymph node status change treatment plan?	
	No	Yes
Chemo & radiation given due to positive Nodes	0	4
Chemo given due to positive nodes	0	11
Chemo given due to positive nodes -SWOG trial	0	1
Low Oncotype ^a	3	0
Low Oncotype -SWOG trial ^b	2	0
Mammoprint low risk ^c	1	0
Medical problems; died a few months later	1	0
Noncompliant; (declined radiation when it was offered)	1	0
Patient was supposed to get chemo but had cardiac arrest	1	0
Radiation because of positive node; no chemo because of low oncotype	0	3
Radiation due to positive nodes	0	1
Total:	9	20

Date of Treatment.
^a 2013, 2017, 2017.
^b 2014; 2015.
^c 2018.

Table 4
High-risk positive lymph nodes treatment alterations.

Changes to treatment plan based on lymph node status	Did lymph node status change treatment plan?	
	No	Yes
Chemo & radiation due to high mammoprint	1	0
Chemo & radiation given due to positive Nodes	0	3
Chemo & radiation given due to positive nodes & mastectomy	0	1
Chemo & radiation -mastectomy due to high oncotype ^a	1	0
Chemo & radiation -mastectomy due to positive nodes	0	36
Chemo due to high oncotype ^b	2	0
Chemo due to HER2	2	0
Chemo given due to positive nodes	0	38
Due to low oncotype score ^c	1	0
Mammoprint high risk ^d	1	0
No radiation/chemo given due to comorbidities	5	0
No treatment due to age	2	0
No treatment due to low oncotype	2	0
Patient lost to follow up	1	0
Patient passed before treatment	1	0
Patient refused treatment	7	0
Radiation due to positive nodes	0	12
Radiation due to positive nodes – no chemo due to low mammoprint	0	1
Radiation – mastectomy due to positive nodes	0	1
Total:	26	92

Date of Treatment.

^a 2012.

^b 2010; 2014.

^c 2018.

^d 2015.

all ages. In breast preservation, if lymph node status does not affect the decision on chemotherapy, then the only reason to evaluate lymph nodes is for local control. Women under 70 undergoing lumpectomies receive radiation for local control and women over 70 would only have a 3% axillary recurrence without radiation from the CALGB 9343 trial.^{6,15} If we choose grade 1 tumors ≤ 2 cm or grade 2 tumors ≤ 1 cm to avoid axillary staging (Mayo low-risk) then there would also be a very low rate of axillary positivity.

Limitations of the current study include its retrospective nature as well as a relatively small sample size. Retrospective studies cannot establish causation, only correlation. If this study was conducted on a larger sample size, then it could have closer approximated the population. Another limitation of the study is the change in treatment recommendations over the time period of this study. These changes in the standard of care over time could influence the type of treatments utilized and affect the results. Additionally, since data was abstracted from a single-surgeon practice, the changes in adjuvant treatment may not be widely applicable, as it potentially reflects the practice of a small cohort of medical oncologists and radiation oncologists who may or may not comply with national recommendations.

Conclusions

This study suggests that the Mayo Clinic rule is reproducible among women with clinically node negative, hormone receptor positive breast cancers. Nearly 50% of women with hormone receptor positive breast cancer fall into the low-risk category and could potentially avoid axillary staging, but 7% (over 70) to 12% (under 70) of those patients will have unexpected positive lymph nodes. This continues to be of importance if the knowledge of lymph node status alters the patient's post-surgical treatment leading to adjuvant chemotherapy and/or radiation therapy. On the other hand, the unexpected rate of positive nodes in low-risk women may be acceptable, if it has no impact on treatment or outcome.

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