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EDITORIAL – BREAST ONCOLOGY

Has the Time Come to Stop Surgical Staging of the Axilla for All Women Age 70 Years or Older with Hormone Receptor-Positive Breast Cancer?

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Classically, for patients with invasive breast cancer, surgical management has included axillary staging. Historically, this was performed by axillary lymph node dissection (ALND). Currently, for clinically node-negative disease, sentinel lymph node (SLN) surgery is routinely used to assess the status of the axilla and to determine whether the patient is pathologically node-positive or node-negative.

Axillary surgery does not directly improve survival, and because ALND is associated with significant morbidity, its role in the setting of SLN-positive disease has evolved over time so that ALND is avoided for women with low-volume axillary disease undergoing breast conservation with adjuvant whole-breast radiation.[1–3]

For patients with a clinically negative axilla, surgical staging with SLN surgery has been the standard for all patients with invasive breast cancer. However, it is important to question this surgical dogma continually, evaluating the advantages and disadvantages of this treatment and the importance of the information obtained on surgical, systemic, and radiation therapy recommendations.

The American Board of Internal Medicine's Choosing Wisely campaign[4] has garnered input from more than 70 medical societies to generate more than 400 recommendations to reduce waste in the health system and avoid risks associated with unnecessary treatment. The Society of Surgical Oncology (SSO) recently announced its five recommendations, the first of which is "do not routinely perform SLN surgery for women older than 70 years with hormone receptor-positive (HR+) breast cancer."[5] Quite correctly, the SSO points out that for these patients who have HR + disease treated with hormonal therapy, SLN surgery neither provides locoregional control nor has an impact on breast cancer mortality.

Breast cancer incidence increases with age, and thus, the highest incidence of breast cancer falls in the group of women age 70 years or older. These women generally have more comorbidities, a shorter life span, and greater risk for side effects from chemotherapy that might be delivered based on information from axillary surgery. Although age alone may not be the best factor for determining which patients may forego axillary staging, the SSO's Choosing Wisely recommendation to avoid routine axillary staging for women age 70 years or older with HR+ breast cancer incorporates tumor biology by limiting to HR+ tumors for which adjuvant endocrine therapy will be recommended together with chronologic age.

With institutional review board approval, we reviewed data from both the National Cancer Database (NCDB) (2004–2013) and Mayo Clinic Rochester (October 2008 to July 2016) to evaluate the current management and frequency of nodal positivity in this patient group. The data showed that 13.4% of the patients in the NCDB and 8.8% of the patients at Mayo meeting these criteria did not have surgical staging of the axilla, demonstrating that the vast majority of women age 70 years or older with

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HR+ disease have been undergoing surgical axillary staging. Of those who underwent axillary surgery, 15.2% of the patients in the NCDB and 14.3% of the Mayo cohort were found to be node-positive. As expected, in both the NCDB and the Mayo data, the proportion of node-positive women was greater with advancing clinical T-stage and also with higher-grade disease. For the patients with T2 or greater disease, the rate of nodal positivity was 29.1% in the NCDB and 26.2% at Mayo.

Our findings are similar to those previously reported by Chagpar et al.[6] for 700 women from the North American Fareston versus the Tamoxifen Adjuvant (NAFTA) trial, which included 93 academic and private medical centers from 1998 to 2002. These authors reported that 6.9% of the women did not have lymph node evaluation, and among those who did, 16% had positive nodes. They proposed a prediction rule to identify women at low risk of nodal disease for whom SLN surgery could potentially be avoided. Further work combining this data set with the AAMC/East Carolina University (AAMC/ECU) Sentinel Lymph Node Project, including data from 16 medical centers from 1996 to 2005,[5,7] showed that age was in fact not linearly associated with risk of axillary nodal involvement. Lymph node metastases were found to be highest in young women, then to decrease until the age of 60 years, after which the incidence plateaued before slightly increasing among women older than 75 years.

One single-institution retrospective review of 140 patients age 70 years or older who had clinical T1-2N0 breast cancer treated with lumpectomy but no SLN surgery demonstrated low axillary recurrence rates and low mortality. The most common cause of death was ischemic heart disease, but the median age of this cohort was 83 years.[8] Tumor size was shown to correlate with survival. These data suggest that life expectancy rather than chronologic age may be a more appropriate factor for clinicians to consider when deciding on treatment and on use or avoidance of SLN surgery. However, life expectancy can be more difficult to judge and more challenging to discuss with patients.

A retrospective study from Italy showed no difference in breast cancer mortality with or without ALND for women age 70 years or older, although the axillary recurrence rate was higher in the no-ALND group (5.8%, 30/499) than among the patients who underwent ALND (0%).[9] A prospective randomized trial in Italy comparing ALND with no ALND among women ages 65–80 years who had cT1N0 disease treated with breast conservation and whole-breast radiation and tamoxifen confirmed these findings, with no difference in survival. The axillary relapse rate was 6% for the no-ALND patients in the trial.[10]

One prospective randomized study, the International Breast Cancer Study Group Trial 10-93, evaluated this question by randomizing women age 60 years or older with tumors larger than 2 cm to ALND or no ALND.[11] The axillary recurrence rate did not differ significantly between the no-ALND group (3%) and the ALND group (1%) during the 6-year follow-up period, and the two groups did not differ in terms of disease-free or overall survival.

These trials, mainly limited to patients with smaller tumors, compared ALND and no ALND because ALND is associated with comorbidities and is known not to have an impact on survival. However, because the surgical landscape has changed and SLN surgery is routinely used, the risk benefit balance differs between SLN surgery and ALND for staging among these women.

Nodal status remains influential in guiding systemic therapy and radiation recommendations potentially even more so for this group of women whose comorbidities are greater, and physicians strive to avoid both over- and undertreatment.

ADJUVANT RADIATION THERAPY RECOMMENDATIONS

Surgery and radiation are important for locoregional control of breast cancer. Increasingly, surgery is becoming less invasive, especially when adjuvant radiation therapy is part of the treatment plan. However, pathologic information, especially nodal staging obtained at surgery, is a key driver in deciding whether radiation is needed and which nodal basins, if any, should be included in the radiation field.

In Cancer and Leukemia Group B 9343, women older than 70 years with estrogen receptor-positive (ER+) disease were treated with tamoxifen and randomized to whole-breast radiation or no radiation. Only 38% of the patients in that study underwent ALND.[12] Among the patients who did not have ALND, those treated with tamoxifen and radiation had no axillary recurrences and 6 (3%) of 200 patients in the tamoxifen-only group had axillary recurrence. However, 98% of the patients in this trial had tumors 2 cm in size or smaller.

In a randomized study of adjuvant tamoxifen with or without radiation for patients age 50 years or older, 476 women age 65 years or older showed a nonsignificant trend toward a higher axillary recurrence rate when axillary dissection was omitted (3.3% in the tamoxifen group vs 0.6% in the tamoxifen plus radiation group; $p = 0.07$).[13]

The American College of Surgeons Oncology Group Z0011 study demonstrated that patients with one or two positive SLNs who receive whole-breast irradiation can avoid ALND[1] without compromising survival. However, it should be noted that although the trial guidelines specified that radiation should be directed to the breast only, up to 20% of the patients also had regional nodal irradiation. As expected, regional nodal irradiation was more commonly

delivered to patients at higher risk for additional nodal involvement.[14] Whether the regional nodal irradiation had any impact on disease-free or overall survival could not be determined because it was not applied in any systematic or randomized manner. However, nodal status was known and available for planning adjuvant radiation and systemic recommendations.

However, several recent studies have demonstrated that regional nodal irradiation has a significant impact for patients with relatively early-stage node-positive breast cancer. Specifically, two recent papers published in the *New England Journal of Medicine* demonstrated a significant advantage of regional nodal irradiation for node-positive patients. Both the Canadian MA.20 trial[15] and the European Organisation for Research and Treatment of Cancer (EORTC) trial[16] randomized patients to breast–chest wall irradiation alone or breast–chest wall irradiation plus regional nodal irradiation. A majority of the patients in these trials had fewer than four involved lymph nodes. Although these trials did not reach their primary goal of demonstrating statistically significant improved survival, they both reported an improvement in locoregional control as well as disease-free and distant metastasis-free survival in the groups randomized to regional nodal irradiation.

Although a woman older than 70 years with node-positive breast cancer may be less likely to realize a survival benefit from regional nodal irradiation, those without significant comorbidities and long life expectancy may derive significant locoregional control as well as a disease-free and/or distant metastasis benefit from regional nodal irradiation. Although the majority of the women in the two recently published randomized trials underwent ALND, it is reasonable to assume that an SLN-positive patient will derive a similar benefit. Therefore, diagnosis of a positive SLN can influence regional nodal irradiation treatment decisions and ultimately have an impact on both locoregional control and disease-free survival. For those women at significant risk for nodal involvement, with low comorbidities and long life expectancy, SLN sampling is a reasonable management strategy that can have an impact on patient outcomes.

Just as documentation of nodal positivity is important for guiding treatment, pathologic confirmation of nodal negativity may be important for avoiding consideration of axillary radiation due to the unknown nodal status.

ADJUVANT SYSTEMIC THERAPY RECOMMENDATIONS

Classically, information about nodal status has been used by medical oncologists to make treatment recommendations regarding chemotherapy. However, a wealth of data currently demonstrate that "biology trumps stage" with regard to chemotherapy benefit for patients with ER+ breast cancer, the most common subtype of breast cancer among the elderly. Thus, because regional nodal involvement is not a predictor of response to therapy for ER+ breast cancer, genomic predictors are increasingly used to guide adjuvant chemotherapy decisions. Multiple studies have demonstrated that multi-gene panels can identify patients with not only the highest risk of recurrence but also the greatest benefit of chemotherapy.[17,18] Furthermore, given that age is an independent risk factor associated with higher risk of serious chemotherapy-related side effects in the elderly,[19] many physicians recommend adjuvant endocrine therapy as the only systemic therapy for a woman 70 years of age or older.

In this setting, an important question arises: "Does axillary staging have a role for women age 70 years or older?" Recently, an Oxford overview analysis of more than 46,000 women focusing on the risk of late distant recurrence showed that nodal status was the major driver of late distant recurrence.[20] Specifically, compared with a distant risk of approximately 10% for those with negative lymph nodes, the risk for late distant recurrence (after 5–14 years) was nearly 16% for those with one to three positive lymph nodes and 28% for those with four to nine positive lymph nodes. Given that multiple studies have demonstrated a 20–40% reduction in recurrence risk when adjuvant hormonal therapy is extended to years 5–10,[21–23] with the greatest absolute benefit observed for those with positive lymph nodes,[24] the recommendation to extend adjuvant hormonal therapy may be increasingly based on the presence or absence of nodal status obtained from surgical staging.

A review showed that the average expected life span is 86 years for a 70-year-old woman and 89 years for a 75 year-old woman (calculated from social security.gov). Based on these data, women age 70 years or older who did not undergo axillary staging and are alive after completing 5 years of adjuvant hormonal therapy may be denied extended adjuvant hormonal therapy given a presumed low risk of future distant events.

In summary, although chronologic age and tumor biology are major factors influencing the decision to administer chemotherapy after breast surgery, for women age 70 years or older with HR+ disease, information derived from nodal status remains an important factor for tailoring decisions regarding both adjuvant endocrine and radiation therapy. The question really becomes what proportion of node-positive patients are we willing to consider under staging by avoiding axillary surgery. For women age 70 years or older with HR+ disease, the rate of nodal positivity is about 15%. Would more specific criteria allow identification of a subset of patients at higher risk for nodal

metastases to undergo SLN and enable us to avoid SLN surgery for a lower-risk subgroup of these women? In addition to patient age and tumor biology, factors such as tumor size and grade also may be an important part of this decision. For a 72-year-old woman with a 4-cm grade 3 tumor, SLN staging may be very reasonable, whereas for a 72-year-old woman with a 1-cm grade 1 tumor, avoiding SLN surgery may be the better option.

Reevaluating and questioning our daily practice is important to ensure that we are continually doing the best for our patients. Just doing something because we can or because we have always done it is not reason enough to continue doing it. We agree with SSO that the time has come to reconsider the use of routine SLN for women age 70 years or older with HR+ disease, particularly for those with a low risk of nodal positivity. However, identification of patients with nodal involvement remains important for adjuvant radiation and systemic treatment planning, and chronologic age alone may not be the optimal algorithm for exclusion of SLN. We recommend that further research be performed for proper individualization of SLN surgery for women age 70 years or older with HR+ disease before it is eliminated altogether.

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