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Does lymph node status influence adjuvant therapy decision-making in women 70 years of age or older with clinically node negative hormone receptor positive breast cancer?

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ABSTRACT

Background: Women ≥70 years old with clinically (c) lymph node (LN) negative (−), hormone receptor (HR) positive (+) breast cancer are recommended not to be routinely staged with a sentinel LN biopsy. We sought to determine how this affects adjuvant decision-making.

Methods: Statistical analyses were performed to determine the association of LN evaluation with adjuvant chemotherapy and radiation therapy in cLN-, HR + breast cancer patients in the National Cancer Database.

Results: Between 2004 and 2013, there were 193,728 patients aged 70–90 with cLN-, HR + breast cancer; 15.0% were LN+. LN + patients were more likely to receive chemotherapy (28.3% vs. 5.5%, $p < 0.001$), hormonal therapy (83.6% vs. 71.4%, $p < 0.001$), post-lumpectomy radiation therapy (81.4% vs. 73.6%, $p < 0.001$) and post-mastectomy radiation therapy (30.3% vs. 5.1%, $p < 0.001$).

Conclusion: 15% of patients aged 70–90 will be LN+. These patients more frequently receive systemic and radiation therapy. LN status may affect treatment in these patients.

Summary: In its 2016 "Choosing Wisely" guidelines, the Society of Surgical Oncology made the recommendation that women ≥70 years of age with clinically lymph node (LN) negative (−), hormone receptor (HR) positive (+) breast cancer should not routinely be staged with a sentinel LN biopsy (SLNB). In this study of 193,728 patients in the National Cancer Data Base who were between the ages of 70 and 90 when they were diagnosed with clinically LN-, HR + invasive breast cancer, we found that 15% were found to be LN+, and that LN status was significantly associated with adjuvant systemic and radiation therapy administration independent of other factors including age, tumor size, grade and comorbidities.

1. Introduction

Over 30% of all invasive breast cancers are diagnosed in women over the age of 70.[1] These patients are more likely to present with favorable, small, low grade tumors that are typically node negative and hormone receptor positive (HR+) that are responsive to endocrine therapy.[2,3] These elderly patients are also more likely to have comorbidities which may limit the use of systemic chemotherapy.[3] Given the perception of limited utility for surgical staging by axillary lymph node (LN) evaluation in this cohort, some have proposed that perhaps sentinel LN biopsy (SLNB) could be avoided in some elderly patients.[4–6] More recently, the Society of Surgical Oncology (SSO) has proposed, as part of the "Choosing Wisely" campaign, that surgeons "don't routinely use sentinel node biopsy in clinically node negative women ≥ 70 years of age with HR + invasive breast cancer".[7] Previous reports have noted that 14–16% of these patients will have positive nodes.[4,8] Knowledge of this positive LN status may impact adjuvant therapy decisions. Hence, prior to adopting the SSO's recommendation, we sought to

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determine the impact of omission of SLNB in clinically LN-, HR + breast cancer patients 70 years of age or older.

2. Methods

The National Cancer Database (NCDB) is a resource jointly sponsored by the American College of Surgeons and the American Cancer Society, which captures data from over 1500 Commission on Cancer (CoC)-accredited facilities, representing more than 70% of all newly diagnosed cancers in the United States. This database was queried for patients with clinically LN-, HR + invasive breast cancers diagnosed at the age of 70 or older between 2004 and 2013. During this time period, sentinel node biopsy was generally considered standard of care for this patient population. Statistical analyses were performed to determine the impact of LN evaluation on receipt of adjuvant systemic chemotherapy and radiation therapy using SPSS Version 22 software.

3. Results

Between 2004 and 2013, there were 193,728 patients in the NCDB who were between the ages of 70 and 90 (median age, 77) when they were diagnosed with clinically LN-, HR + invasive breast cancer. Patients over the age of 90 are categorically grouped together in the NCDB; as we wished to evaluate age as a continuous variable, those over the age of 90 were excluded from the analysis. The median tumor size was 14 mm. 63.6% of patients had a lumpectomy, 31.4% had a mastectomy, and 4.9% had no surgery for their primary breast cancer. 154,504 patients (79.8%) had regional LN surgery; of these, the median number of LNs examined was 3 (range; 0–88). Factors correlating with LN evaluation are shown in Table 1.

Of the patients who had LN evaluation, LN status was unknown in 30 (0.01%). Of the remaining 154,474 patients, 23,138 (15.0%) were found to be LN+. Among the LN + patients, the median number of positive LNs was 1 (mean = 2.6; 95% CI: 2.5–2.6). Factors correlating with LN status are shown in Table 2.

3.1. Systemic therapy

The majority of patients in this cohort (n = 129,376; 66.8%) received hormonal therapy; only 14,479 (7.5%) received chemotherapy. Information on chemotherapy or hormonal therapy was missing in 7183 (3.7%) and 7924 (4.1%) of patients, respectively. Of the 181,214 patients for whom this information was available, 52,578 (29.0%) of patients received neither modality; 11,430 (6.3%) received both. Factors correlating with the use of systemic therapy are shown in Table 3. Patients who had LN evaluation and those who were LN+ were more likely to receive chemotherapy (9.0% vs. 2.7%, $p < 0.001$ and 28.3% vs. 5.5%, $p < 0.001$, respectively). These patients were also more likely to receive hormonal therapy (73.3% vs. 54.9%, $p < 0.001$ and 83.6% vs. 71.4%, $p < 0.001$, for LN evaluation vs. not and LN + vs. LN-, respectively). On multivariate analysis, controlling for patient age, comorbidities (measured by Charlson-Deyo score), race, ethnicity, income, insurance status, community size, region, tumor size, grade, and primary surgery type, lymph node evaluation remained an independent factor that was positively correlated with the use of chemotherapy (OR = 2.230; 95% CI: 2.060–2,501, $p < 0.001$). Positive lymph node status was similarly found to be an independent predictor of chemotherapy use (OR = 5.412; 95% CI: 5.165–5.671, $p < 0.001$). Similarly, in two separate multivariate analyses, controlling for all of the factors mentioned above, lymph node evaluation (OR = 1.829; 95% CI: 1.771–1.888, $p < 0.001$) and positive lymph node status (OR = 1.924; 95% CI: 1.506–2.546, $p < 0.001$) each remained an independent factor that was positively correlated with the use of hormonal therapy. When the use of hormonal therapy was included in the multivariate analyses, lymph node evaluation and positive lymph node status remained an independent predictor for use of chemotherapy ($p < 0.001$ for each).

3.2. Radiation therapy

In this cohort of clinically LN-, HR + patients, 123,135 underwent a lumpectomy for their primary tumor. Of these, 80,622 (66.3%) had adjuvant radiation therapy. Of the 59,888 patients who underwent a mastectomy, 6220 (10.4%) received post-mastectomy radiation therapy. Factors associated with receipt of radiation therapy post-lumpectomy and post-mastectomy are shown in Table 4. Patients who underwent LN evaluation, and those who were LN+, were both more likely to undergo post-lumpectomy radiation therapy (81.4% vs. 73.6%, $p < 0.001$) and post-mastectomy radiation therapy (30.3% vs. 5.1%, $p < 0.001$). On multivariate analysis, controlling for patient age, comorbidities (measured by Charlson-Deyo score), race, ethnicity, income, insurance status, community size, region, tumor size, grade, receipt of hormonal therapy, and distance from patient's residence to closest radiation facility, lymph node evaluation remained an independent factor that was positively correlated with the use of radiation therapy after lumpectomy (OR = 3.980; 95% CI: 3.825–4.142, $p < 0.001$). Positive lymph node status was similarly an independent predictor of receipt of radiation therapy after lumpectomy on multivariate analysis (OR = 1.408; 95% CI: 1.325–1.497, $p < 0.001$). On multivariate analysis including all of the covariates above, LN evaluation was an independent factor that was positively correlated with receipt of post-mastectomy radiation therapy (OR = 2.198; 95% CI: 1.888–2.558, $p < 0.001$), as was LN positivity (OR = 5.874; 95% CI: 5.484–6.293, $p < 0.001$).

4. Discussion

Nearly a third of all invasive breast cancers diagnosed in the United States occur in women aged 70 years or older,[1] yet this subpopulation of patients has traditionally been omitted from clinical trials. While there may be a perception of greater comorbidities in the elderly, the average 70-year old woman will have an additional life expectancy of 17.5 years.[9] In our study, we found that the majority of patients aged 70–90 with clinically LN-, HR + had no significant comorbidities, i.e., a Charlson-Deyo score of 0. Their tumors tended to be small and well-to-moderately differentiated. Over 95% of patients in this cohort had surgery for their primary cancer, and nearly 80% had some form of LN evaluation. This is roughly twice the rate of SLNB reported in a prospective population-based Swiss study,[10] and may reflect a US bias towards more aggressive therapy.

It has long been known that LN evaluation does not impact survival[11]; the two main purposes of LN evaluation are staging and local control. Martelli et al., in their study of 238 patients aged 65–80 with cT1N0 breast cancer randomized to axillary dissection versus no axillary staging found no difference in survival between the two groups; 15-year axillary recurrence rates were 0% vs. 5.2% in the two groups, respectively.[5] It may also be argued that staging the axilla is less likely to impact adjuvant therapy decisions in elderly patients with clinically LN- and HR + disease; hence the SSO has recommended that SLNB not be part of the routine management of these breast cancer patients.[7] Indeed, a number of investigators have found that elderly patients are less likely to undergo SLNB, and many have also found that they are less likely to undergo aggressive adjuvant therapy.[10,12,13] In our study, we found that patients who had LN evaluation, and those who were

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