

Distant Metastasis in Elderly Patients with Breast Cancer: Prognosis with Nodal Status

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INTRODUCTION

As our population ages, the number of elderly individuals diagnosed with breast cancer will continue to increase. Currently, the median age at diagnosis for breast cancer patients is 61 years (American Cancer Society, 2006), and women aged 75–79 years have the highest incidence rate of this disease. Despite the considerable number of elderly breast cancer patients being diagnosed today, these patients have traditionally been excluded from clinical trials (Goodwin *et al.*, 1988; Trimble *et al.*, 1994), and therefore controversy remains regarding what constitutes optimal therapy for this population. Certainly, the elderly form a distinct subgroup of patients, in whom tumor biology, comorbidities, and competing risks must be considered in weighing treatment decisions. However, with advances in medical management, our population continues to enjoy ever-increasing longevity, and therefore many elderly patients with breast cancer may still be expected to have a reasonable

quantity and quality of life. Therefore, it behooves clinicians to consider a variety of factors influencing survival and progression to distant metastasis, and manage patients accordingly.

While it is well-known that lymph node status is one of the strongest predictors of prognosis, the need for lymph node evaluation in elderly patients has been a source of significant debate. Older literature points to the concept that axillary node dissection may lead to increased lymphedema in this population, and that adjuvant treatment may not change regardless of lymph node status. With the advent of sentinel node biopsy, a minimally invasive technique to accurately stage the axilla, the concept of lymph node evaluation in the elderly population with breast cancer is being revisited.

BREAST CANCER IN THE ELDERLY

The “elderly”, variably defined in the literature as patients older than 65, 70 or 80

years of age, is becoming an increasing demographic population of breast cancer patients. Women aged 75–79 years have the highest incidence rate of breast cancer (496.6 cases per 100,000), and while the incidence rate of breast cancer has plateaued for all other age categories, the incidence rate of this disease continues to climb in those over the age of 50 (American Cancer Society, 2006). Despite being a significant subpopulation of breast cancer patients, the elderly remain understudied. They are less likely to be included in clinical trials, and it is difficult to extrapolate findings in younger patients to the elderly who have unique issues (both in terms of breast cancer tumor biology and other comorbidities and competing risks) which need to be considered in treatment planning.

Tumor Biology

It has been argued that elderly patients with breast cancer may have a biologically different disease than their younger counterparts (Djordjevic *et al.*, 2004). A number of studies have found that older patients tend to have larger tumors at the time of diagnosis. For example, Djordjevic *et al.* (2004) found that 75% of patients younger than 65 years of age had tumors < 2 cm, whereas only 62% of patients 65 years of age and older had tumors that were < 2 cm. Similarly, Davis *et al.* (1985) found that 59% of patients 80 years of age or older presented with Stage II–IV breast cancer. Some authors, however, have found that Stage I lesions are equally common across age groups (Mueller *et al.*, 1978), while others have found that elderly patients tend to have more localized tumors than younger patients (Herbsman

et al., 1981). In a study by Hunt *et al.* (1980), the majority of elderly patients had larger local tumors, but did not have regional or distant metastasis, leading to the speculation that a “nonmetastasizing variant” of breast cancer may be more common in the elderly population.

In addition, older patients tend to have estrogen receptor positive (ER+) tumors, and may therefore be adequately treated with hormonal therapy. Djordjevic *et al.* (2004) found that 68% of older patients had ER+ disease, whereas only 28% of younger patients were ER+. Given that the majority of older patients have less aggressive, ER+ breast cancers that can be adequately treated with hormonal therapy, some authors have argued that lymph node evaluation in these patients is unnecessary as it will not change management. Therefore, consistently across studies, a significant minority of elderly patients have not been adequately staged as no form of lymph node evaluation has been performed.

Patient Comorbidities

While patient comorbidities are often cited as a factor influencing the decision not to pursue lymph node evaluation, some have found that less optimal surgery did not always correlate with the degree of comorbid conditions (Law *et al.*, 1996; Greenfield *et al.*, 1987). Some studies have demonstrated that morbidity of surgical interventions in this population is related primarily to the wound (Hunt *et al.*, 1980; Djordjevic *et al.*, 2004), and, therefore, the addition of sentinel node biopsy would be anticipated to add little to the morbidity of the surgical extirpation of the tumor. Other studies have found that morbidity

and mortality of breast cancer surgery are comparable between patients 80 years of age or older and their younger counterparts (Davis *et al.*, 1985; Swanson *et al.*, 1991). While elderly patients often face competing risks, it has been shown that their disease-specific survival is not significantly different from younger patients (Herbsman *et al.*, 1981; Djordjevic *et al.*, 2004; Crowe, Jr. *et al.*, 1994). Therefore, chronologic age alone should not be a deterrent to appropriate treatment of breast cancer patients.

DETERMINANTS OF DISTANT METASTATIC DISEASE

It is well-accepted that breast cancer survival is determined primarily by distant metastatic disease. As most elderly patients have ER+ disease, and are managed with adjuvant hormonal therapy, there is a need to identify the determinants of early distant metastatic disease, the presence of which may precipitate the use of more aggressive systemic chemotherapy in patients deemed fit enough to tolerate such a regimen.

In a study of 938 patients ≥ 65 years of age treated in a multicenter prospective randomized controlled trial of tamoxifen versus toremifene for adjuvant therapy of breast cancer, it was found that 17 patients (1.8%) progressed to distant metastatic disease at a median time from diagnosis of 21 months (range: 3–50) (Chagpar *et al.*, 2006). Eight of these patients (47.1%) died of their disease, with a median time to death of 22 months after metastatic disease. Factors predicting the development of metastatic disease in this cohort on univariate analysis included tumor size,

number of positive nodes, lymphovascular invasion, nuclear grade, and progesterone status. On multivariate analysis, the number of positive lymph nodes (as a continuous variable) was the only independent factor which remained predictive of distant metastatic disease ($p = 0.029$). Further analysis demonstrated that patients with 4 or more positive nodes were significantly more likely to develop early metastatic disease than those with 0–3 positive nodes (OR: 20.304, 95% CI: 2.777–148.456, $p = 0.003$).

Similarly, a study of 181 node-positive patients aged 65–84 years treated with tamoxifen vs. placebo found that the number of positive nodes significantly affected the proportion of patients who were disease free at 10 years (Cummings *et al.*, 1993). For example, in the tamoxifen arm alone, 61.9% of patients with 1–3 positive nodes were disease free at 10 years, compared with only 17.6% of patients who had 4 or more positive nodes. These data are echoed by survival data which found, in the tamoxifen treated arm, that patients with 4 or more positive nodes were nearly half as likely to be alive for 10 years than those with 1–3 positive nodes (35.8% vs. 61.0%).

It is not surprising that the number of positive lymph nodes is a key determinant of survival. In 5 previous National Surgical Adjuvant Breast and Bowel Project studies, the rate of distant metastasis in patients with 4 or more positive lymph nodes was found to be nearly twice that of patients who had only 1–3 positive nodes (Taghian *et al.*, 2004). These data argue that it would behoove clinicians to consider lymph node status in determining the prognosis of elderly patients with breast cancer.

Others, however, have argued that lymph node status does not affect disease free survival in patients over 70 years of age. In a study of 378 patients over the age of 70, the only factor affecting 3- and 5-year survival rates was age (Newlin *et al.*, 2002). These data, however, did not relate specifically to disease-specific survival. Interestingly, however, among all the factors analyzed, nodal status was the most significant, with node-positive patients having a worse 5-year survival than their node-negative counterparts (69% vs. 77%, $p = 0.0673$). One could speculate that if the study had increased power, and perhaps if the authors had analyzed the number of positive nodes rather than simply nodal status, a statistically significant association may have been found.

LYMPH NODE EVALUATION IN THE ELDERLY

It has been well-established that axillary node dissection alone does not improve survival (Fisher *et al.*, 2002; Veronesi *et al.*, 2002). However, it is also well-accepted that lymph node status is a significant factor affecting prognosis. Therefore, for the majority of breast cancer patients, lymph node evaluation is considered a standard part of breast cancer surgical management.

In the elderly population, lymph node evaluation is commonly omitted. In a study breast cancer patients 70 years of age or older treated at a community hospital, it was found that complete pathologic staging was performed in only 64% of patients (Litvak and Arora, 2006). Similarly, in a study of 198 patients with breast cancer 80 years of age or older, histologic examina-

tion of the lymph nodes was not performed in 82 patients (41%) (Davis *et al.*, 1985). In a study of 39 Japanese patients over 80 years of age, 6 (15.3%) did not have axillary staging (Morishita *et al.*, 1997), and in a similar study of 325 Polish patients over 70 years of age, 50 (15.4%) did not have axillary staging (Nagadowska and Kulakowski, 1991).

Increasing age is associated with decreased odds of having lymph node evaluation independent of health status, patient preferences, clinical factors, and provider variables (Edge *et al.*, 2002). Furthermore, increased age is associated with decreased adherence to breast cancer treatment guidelines independent of comorbidity score, clinical stage, and tumor characteristics (Giordano *et al.*, 2005).

While a number of authors have found that lymph node evaluation significantly influences subsequent treatment decisions in the elderly population (e.g., McMahon *et al.*, 2005), others point out that lymph node staging is not without morbidity. General anaesthesia is frequently required, and there is a risk of lymphedema, which may be significant for the elderly population. One study found that older patients had an increased risk of lymphedema after axillary surgery than younger patients (16% vs. 13%, $p = 0.02$) (Djordjevic *et al.*, 2004). In addition, one study demonstrated that patients 67 years or older who underwent lymph node evaluation had three times the rate of arm complications 2 years post-treatment than those who did not have any axillary surgery (Mandelblatt *et al.*, 2002). Furthermore, these arm sequelae resulted in lower physical and mental functioning.

With the advent of sentinel node biopsy, however, the risk of lymphedema and

other complications are significantly reduced while still preserving the ability to accurately stage the axilla (Veronesi *et al.*, 2003). In addition, some authors have suggested that this technique can also be performed under local anaesthesia (van Berlo *et al.*, 2003).

Sentinel Node Biopsy Technique

Sentinel node biopsy has become widely accepted as a minimally invasive method to stage the axilla in patients with breast cancer. This technique, which uses the injection of a radioactive colloid and/or a blue dye into the breast, allows for the tracking of the tracer to the first, or “sentinel”, draining lymph nodes in the axilla (Figure 42.1). A number of studies have validated this technique, demonstrating that it is a safe, reliable and accurate means of staging the axilla (Veronesi *et al.*, 2003).

Several authors have specifically evaluated the technique of sentinel node biopsy

in the elderly. In the Mayo Clinic experience, for example, the overall sentinel node identification rate was not significantly different between patients < 70 years of age and those who were ≥ 70 (98.8% vs. 97.1%, $p = 0.11$) (McMahon *et al.*, 2005). Furthermore, in their experience, knowledge of nodal status significantly impacted adjuvant therapy decisions. For example, patients ≥ 70 years of age were more likely to receive systemic cytotoxic chemotherapy if they were sentinel node-positive versus those who were sentinel node-negative (24.0% vs. 2.8%, $p < 0.01$). In addition, sentinel node status significantly correlated with the finding of systemic recurrence, with 8.2% of sentinel node positive patients progressing to distant metastatic disease, versus none of the sentinel node negative patients relapsing ($p < 0.01$).

The Milan group similarly found that sentinel node biopsy could be performed in patients ≥ 70 years of age with a 100% sentinel node identification rate (Gennari *et al.*, 2004). Of the 241 patients in their study, 90 (37.3%) were found to have sentinel node metastasis, each of these patients had an axillary node dissection in the same surgical setting. No major surgical complications were noted in their cohort. Therefore, it appears that sentinel node biopsy is safe and reliable in the elderly population.

With the minimal morbidity of sentinel node biopsy, it would follow that most elderly patients may have lymph node evaluation in this manner. However, for those with exorbitant comorbidities, there may be a subpopulation in whom lymph node evaluation may not be warranted. Several small non-randomized studies found low rates of locoregional failure and no adverse effect on survival in elderly patients with small hormone-responsive

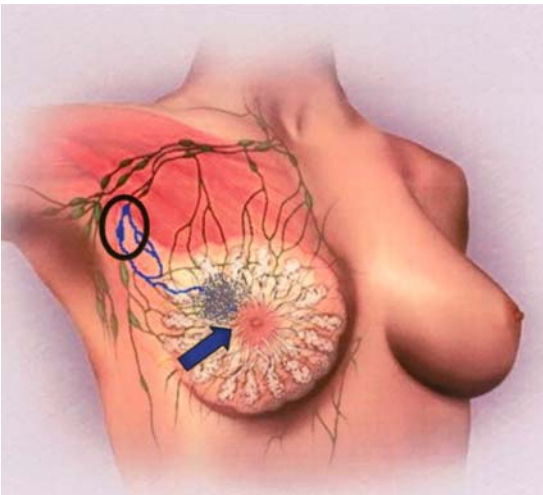


FIGURE 42.1. Arrow indicates injection site. SLNs (shown in blue) are circled. Non-SLNs are shown in green. Grey cloud indicates tumor.

tumors and clinically negative axillae in whom lymph node evaluation was omitted (Feigelson *et al.*, 1996; Martelli *et al.*, 2003). A randomized controlled trial comparing axillary dissection to no axillary dissection in patients 65–80 years of age with clinical T1N0 breast cancer found that 2/110 (1.8%) patients who did not undergo axillary dissection went on to develop clinically apparent axillary disease (Martelli *et al.*, 2005). With a median follow-up of 60 months, the two groups were similar in terms of overall mortality, breast cancer mortality, and breast cancer events (including ipsilateral breast cancer recurrence, contralateral breast cancer and distant metastasis). While these results suggest that some elderly patients with low risk cancers may be spared lymph node evaluation, doing so could result in suboptimal local control and staging for some patients who may have benefited from axillary node dissection and systemic therapy.

In order to address the issue of predicting which elderly patients will have lymph node metastasis, a clinical prediction rule was recently presented (Chagpar *et al.*, *American Society of Breast Surgeons*, 2007). This statistical model, based on a multivariate analysis, predicts the likelihood of lymph node metastasis in patients ≥ 70 years of age with hormonally sensitive tumors. The model, based on patient age, tumor size, and lymphovascular invasion, was found to predict a group of patients with a 5% likelihood of having lymph node metastasis. While this model was validated in an independent test set, and may be useful in predicting the likelihood of lymph node metastasis in elderly patients with significant comorbidities, it should not be used in lieu of sentinel node biopsy in patients at good operative risk.

In conclusion, the elderly represent a distinct subpopulation of breast cancer patients, who may have a unique tumor biology, and certainly present with a multitude of comorbidities which must be taken into account when planning management of their malignancy. However, while this population may have its own particular challenges, it has been well-established that the elderly are frequently undertreated, and this may have implications in terms of their overall survival and progression to distant metastatic disease.

One of the most significant predictors of early systemic metastasis in elderly patients is the number of positive lymph nodes. However, lymph node evaluation is frequently omitted in these patients. With the advent of sentinel node biopsy, the axilla may be accurately staged using a minimally invasive procedure with minimal if any morbidity. Therefore, the elderly should not be denied lymph node evaluation on the basis of chronological age alone. For those with significant comorbidities in whom sentinel node biopsy is deemed inappropriate, newer clinical prediction rules may provide some insight into the probability of lymph node metastasis in these elderly patients.

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