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Regional recurrence in the era of sentinel lymph node biopsy

Maria E. Linnaus, M.D.[a], Amylou C. Dueck, Ph.D.[b], Heidi E. Kosiorek, M.S.[b], Richard J. Gray, M.D.[a], Nabil Wasif, M.D.[a], Donald W. Northfelt, M.D.[c], Karen S. Anderson, M.D., Ph.D.[c], Ann E. McCullough, M.D.[d], William W. Wong, M.D.[e], Michele Y. Halyard, M.D.[e], Samir H. Patel, M.D.[e], Barbara A. Pockaj, M.D.[a,*]

[a]Department of General Surgery, Mayo Clinic, 5777 East Mayo Boulevard, Phoenix, AZ, 85054, USA; Departments of [b]Biostatistics, [c]Oncology, [d]Pathology and [e]Radiation Oncology, Mayo Clinic, Phoenix, AZ, USA

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Abstract

BACKGROUND: The incidence of all-location regional recurrence after sentinel lymph node biopsy is not well documented. This study attempts to identify risk factors.

METHODS: A prospectively maintained database was queried to identify patients with a regional recurrence of breast cancer after a first operation for invasive unilateral breast cancer. Patients with regional recurrence were compared with those alive and disease free at 5 years.

RESULTS: Twenty-one of 1,060 patients (2%) experienced a regional recurrence. Most patients (95%) underwent sentinel lymph node biopsy as their axillary staging. Those with regional recurrences had larger tumors ($P < .001$), higher stage disease ($P < .001$), more estrogen receptor– and triple-negative breast cancers ($P < .001$), and more positive lymph nodes ($P = .007$). Mastectomy ($P = .001$) and receipt of neoadjuvant and/or chemotherapy ($P < .001$) were more common among those with regional recurrences.

CONCLUSIONS: Regional recurrence of breast cancer occurs infrequently. Risk factors include high-risk cancers, higher stage at presentation, nodal involvement, and need for therapies reflecting higher risk biology.

Sentinel lymph node (SLN) biopsy was introduced as a modality of axillary staging for breast cancer in 1994 after previous studies demonstrated success in cases of melanoma.[1] Before the introduction of SLN biopsy, axillary lymph node dissection (ALND) was routinely used for axillary staging in breast cancer. Although once considered the gold standard for axillary staging, ALND is associated with high morbidity. SLN biopsy has been found to produce equivalent results in the clinically node negative axilla as ALND without the same morbidity.[2–4] Therefore, SLN biopsy has replaced routine ALND for the clinically negative axilla in breast cancer.

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* Corresponding author. Tel.: +1-480-342-2849; fax: +1-480-342-2866.

E-mail address: pockaj.barbara@mayo.edu

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Most regional recurrences in breast cancer are in the ipsilateral axilla and supraclavicular nodes and, less commonly, the internal mammary nodes.[5] The median time from initial treatment to regional recurrence ranges from 20 months to 3.1 years.[6,7] Historically, breast cancer patients who develop a regional recurrence have worse survival compared with those without a regional recurrence.[6,8] ALND is associated with a low rate of regional recurrence.[9–13] New studies evaluating SLN biopsy have demonstrated a similar low rate of regional recurrence focusing on ipsilateral axillary recurrences.[14–18]

Risk factors for regional recurrence have been well documented in patients who have undergone ALND. These include tumor size, grade, lymphovascular invasion, and increasing number of positive lymph nodes.[5,19] Triple-negative tumor biomarkers have also been shown to increase the risk of regional recurrence compared with the estrogen receptor (ER)– and progesterone receptor–positive tumors.[20,21] Although these risk factors have played a consistent role historically, there have been numerous advances in the surgical, radiation, and medical management of breast cancer that may have affected the risk factors contributing to the development of regional recurrence. There are few studies documenting the risk factors in this current era of management. In particular, the use of SLN biopsy may improve surgical accuracy in pathologic staging, and the addition of regional nodal irradiation in high-risk patients affects outcomes.[22,23] The individualization and improvement of chemotherapy regimens have also been significant in the modern treatment of breast cancer. In this study, we aim to determine if traditional risk factors still play a role in regional recurrence during this era of routine SLN biopsy.

Methods

Institutional Review Board approval was obtained for retrospective evaluation of a prospective breast cancer patient database to identify patients with a regional recurrence of breast cancer after undergoing a first operation for unilateral invasive breast cancer from 1995 until 2012. All patients with ductal carcinoma in situ, known recurrent disease at presentation, and those with known metastatic disease were excluded. Patients were clinically evaluated at presentation by the treating physician for metastatic disease and additional work-up was performed as clinically indicated. Patient demographics, cancer characteristics, and treatment were analyzed. Of note, evaluation for HER2 amplification was only performed on all patients beginning in 2004.

Patients who presented with clinically suspicious axillary lymph nodes were evaluated preoperatively by the discretion of the treating surgeon. Most patients underwent preoperative ultrasound and confirmatory biopsy, others underwent confirmation by SLN biopsy and frozen sections, whereas others underwent complete axillary dissection. Patients who were treated with preoperative systemic therapy did not undergo pretreatment SLN biopsy. Patients with clinically negative axillas were generally staged with post-treatment SLN biopsy and further axillary staging as determined by SLN status. Those patients with clinically suspicious or positive pretreatment lymph nodes (determined by ultrasound-guided biopsy) usually underwent complete lymph node dissection after treatment with selected patients being offered SLN biopsy.

Patients with stage I/II breast cancer who had breast-conserving surgery were treated with adjuvant whole breast irradiation using 3-dimensional conformal technique. Accelerated partial breast irradiation was offered to selected patients with low risk of nodal recurrence. After the result of Cancer and Leukemia Group B (CALGB) 9343 was reported,[24] patients who were 70 years or older with ER-positive disease were given the option of no radiation. High-risk breast-conserving therapy (BCT) or post-mastectomy patients received adjuvant radiation therapy targeting the whole breast or chest wall with inclusion of the axillary and supraclavicular lymphatic sites. High-risk patients included those with 4 or more positive lymph nodes, positive margins, lymphovascular invasion, or tumors larger than 5 cm. At the discretion of the radiation oncologist, some patients were deemed intermediate risk based on pathological factors (eg, premenopausal with 1–3 positive lymph nodes) and received whole breast radiation with "high tangent" fields including level 1 of the axilla.

Patients were followed by the medical oncologists initially and then transferred to our Survivors' Clinic based on risk of recurrence. History and physical examination were the mainstay of follow-up along with a yearly mammogram. Additional imaging studies were used depending on the patient's clinical history and any new symptoms on follow-up. The National Comprehensive Cancer Network Guidelines were used for follow-up.

Patients with a regional recurrence, observed at any time point, were compared with those who were alive and disease free for at least 5 years. Patients with less than 5-year follow-up time were not included in the latter group. Regional recurrence was defined as a lymph node recurrence presenting in the axillary, supraclavicular, internal mammary, cervical, or interpectoral lymph nodes. Patient and disease characteristics were compared by 2-sample t test for continuous variables and the chi-square analysis for categorical variables. Statistical analysis was performed using SAS software, version 9.3 (SAS Institute Inc., Cary, NC).

Results

Patient characteristics

A total of 1,060 patients from 1995 until 2012 were identified. Twenty-one patients (2%) experienced a regional recurrence. Median follow-up time for those with a regional recurrence was 40.3 months (7.2 to 127.0 months). The