Preoperative MRI Improves Prediction of Extensive Occult Axillary Lymph Node Metastases in Breast Cancer Patients with a Positive Sentinel Lymph Node Biopsy

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Rationale and Objectives: To test the ability of quantitative measures from preoperative dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) to predict, independently and/or with the Katz pathologic nomogram, which breast cancer patients with a positive sentinel lymph node biopsy will have four or more positive axillary lymph nodes on completion axillary dissection.

Materials and Methods: A retrospective review was conducted to identify clinically node-negative invasive breast cancer patients who underwent preoperative DCE-MRI, followed by sentinel node biopsy with positive findings and complete axillary dissection (June 2005–January 2010). Clinical/pathologic factors, primary lesion size, and quantitative DCE-MRI kinetics were collected from clinical records and prospective databases. DCE-MRI parameters with univariate significance ($P < .05$) to predict four or more positive axillary nodes were modeled with stepwise regression and compared to the Katz nomogram alone and to a combined MRI–Katz nomogram model.

Results: Ninety-eight patients with 99 positive sentinel biopsies met study criteria. Stepwise regression identified DCE-MRI total persistent enhancement and volume adjusted peak enhancement as significant predictors of four or more metastatic nodes. Receiver operating characteristic curves demonstrated an area under the curve of 0.78 for the Katz nomogram, 0.79 for the DCE-MRI multivariate model, and 0.87 for the combined MRI–Katz model. The combined model was significantly more predictive than the Katz nomogram alone ($P = .003$).

Conclusions: Integration of DCE-MRI primary lesion kinetics significantly improved the Katz pathologic nomogram accuracy to predict the presence of metastases in four or more nodes. DCE-MRI may help identify sentinel node–positive patients requiring further local-regional therapy.

Key Words: Breast cancer; radiation; MRI; sentinel lymph node; axilla.

For breast cancer patients without clinical axillary lymph node involvement, sentinel lymph node biopsy has become the standard of care for assessing local-regional extent of the disease. It is well agreed on that patients with negative sentinel sampling need no further axillary surgery (1). However, which patients may avoid completion axillary dissection after positive sentinel sampling is an evolving consideration, especially in the setting of adjuvant radiotherapy. Furthermore, optimal design of radiotherapy fields with regard to regional lymphatic coverage is not known.

Very low rates of local-regional recurrence in select sentinel node–positive patients who forego axillary dissection in the setting of planned radiotherapy supports a movement away from completion axillary dissection in low-risk patients. However, low-risk criteria have not been precisely defined (2–7). The rationale behind the increasing tendency to avoid additional surgery is clear—completion axillary dissection carries a 10%–40% risk of lymphedema (8–10), and excellent local control of the axilla has been demonstrated in previous studies with radiation therapy alone (7,11).

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In our current era of practice, patients are increasingly foregoing completion axillary dissection after a positive sentinel lymph node biopsy. The presence of four or more total positive axillary lymph nodes has conferred a higher risk of regional nodal relapse, thus warranting adjuvant radiotherapy to the high axillary and supraclavicular lymph nodes (12). However, without complete pathologic staging information from axillary dissection, the identification of individuals who would benefit from high axilla/supraclavicular lymph node irradiation is less clear. Presently, physicians assess risk of occult disease in the high axilla (and therefore target this area with radiotherapy) using clinicopathologic models such as the Katz nomogram (13). This nomogram is a validated tool to identify patients with a high likelihood of harboring metastatic disease in four or more axillary lymph nodes following a positive sentinel lymph node biopsy. The Katz nomogram incorporates tumor histology, primary tumor size, lymphovascular space invasion, extranodal extension, the number of involved sentinel nodes, the number of uninvolved sentinel nodes, and the size of the largest sentinel node metastasis.

Based on findings that dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) kinetics of primary breast cancers are correlated with axillary lymph node status (14–16), we hypothesized that DCE-MRI will improve our ability to predict the presence of extensive additional axillary disease after a positive sentinel lymph node biopsy and add predictive value to the Katz nomogram. To our knowledge, no published studies have investigated the approach of combining DCE-MRI tumor kinetics features with the Katz nomogram to improve prediction of axillary node involvement. We tested our hypothesis in a retrospective analysis of patients at our center who underwent DCE-MRI, positive sentinel lymph node biopsy, and completion axillary lymph node dissection.

MATERIALS AND METHODS

Following institutional review board approval, a retrospective review was performed of consecutive breast cancer patients with clinically negative axillae who underwent sentinel lymph node biopsy at the University of Washington from June 2005 to January 2010. Subjects were identified through the University of Washington Sentinel Lymph Node Registry, a prospective research database. Patients with biopsy-proven invasive breast cancer who had a positive sentinel node biopsy and completion axillary dissection were eligible for inclusion in this study. Patients were excluded if they received preoperative systemic therapy (chemotherapy, hormonal therapy, or therapy with biologically targeted agents) because of known effects on lesion enhancement (17,18) or did not undergo completion axillary dissection after the positive sentinel node biopsy. All patients were at least 18 years of age and female.

Patients who underwent preoperative/pre-sentinel node DCE-MRI at our institution were then identified through cross-reference with the Consortium Oncology Data Integration (CODI) project database, a solid-tumor clinical research database developed and maintained by the Fred Hutchinson Cancer Research Center in collaboration with the University of Washington. DCE-MRI data for study cases were extracted from the CODI database. Clinical and pathologic features of each case were extracted from the medical record and pathology database.

Pathology

For patients undergoing treatment during the study period, sentinel lymph nodes were routinely sectioned at 2 mm intervals and entirely submitted for histologic examination. Three hematoxylin and eosin (H&E) stained levels were performed and examined on each sentinel lymph node tissue block. Immunohistochemistry with pan-cytokeratin antibodies was performed only in cases with no histologic evidence of metastatic disease on H&E in patients with primary invasive lobular carcinoma.

DCE-MRI Acquisition

All MR examinations were performed on a 1.5 T LX scanner (GE Healthcare, Waukesha, WI) using a dedicated breast coil between June 2005 and December 2009 as described elsewhere (19–22). Scanning protocols follow guidelines established by the American College of Radiology breast MRI accreditation program (23). Imaging sequences included one precontrast and at least two postcontrast T1-weighted three-dimensional fast spoiled gradient recalled series. Before October 2005, scans were performed in the sagittal plane with repetition time/echo time (TR/TE), 6.7/4.2 ms; flip angle, 10°; field of view (FOV), 18–22 cm; slice thickness, 3 mm; and matrix, 256 × 192. From October 2005 through June 2006, scans were performed in the axial plane with TR/TE, 6.2/3 ms; flip angle, 10°; FOV, 32–38 cm; slice thickness, 2.2 mm; and matrix, 350 × 350. Scan time was 90 seconds per acquisition. One precontrast and five postcontrast acquisitions centered at 90, 180, 270, 360, and 450 seconds after injection were obtained. From July 2006, scans were performed in the axial plane with TR/TE, 5.5/2.7 ms; flip angle 10°; FOV 32–38 cm; slice thickness 1.6 mm; and matrix, 420 × 420. Scan time was 180 seconds per acquisition. One precontrast and three postcontrast sequences (centered at 90, 270, and 450 seconds after injection) were obtained. All studies were interpreted by a radiologist fellowship trained in breast imaging.

DCE-MRI Data Analysis

DCE-MRI kinetic parameters were prospectively measured for the primary tumor in each patient at the time of MRI interpretation using a computer-aided evaluation (CAE) program (CADstream; Confirma, Bellevue, WA). The CAE program compares pixel signal intensity values on the precontrast and initial postcontrast scans (centered at 90 seconds). For