Occult metastases in node-negative breast cancer: A Surveillance, Epidemiology, and End Results–based analysis

Charles W. Kimbrough, MD, Kelly M. McMasters, MD, PhD, Amy Quillo, MD, *and* **Nicolas Ajkay, MD,**
Louisville, KY

Introduction. *The role of immunohistochemistry (IHC) for detecting occult lymph node disease in patients initially found to be node-negative by routine pathology is controversial. In this study, we evaluated trends associated with overall survival in node-negative breast cancer patients staged by IHC.*
Methods. *The Surveillance, Epidemiology, and End Results database was queried for all patients with invasive breast adenocarcinoma and negative lymph nodes on routine pathology between 2004 and 2011 who underwent IHC to evaluate for occult nodal disease. Overall survival stratified by N-stage was compared with Kaplan-Meier analysis. Multivariate analysis was performed using a Cox proportional hazards model.*
Results. *Overall, 93,070 patients were identified, including 4,657 patients with isolated tumor cells (<0.2 mm diameter or <200 cells) and 6,720 patients with micrometastases (0.2–2 mm diameter). Kaplan-Meier curves demonstrated a difference in overall survival across all groups (*$P < .0001$*). On multivariate analysis, micrometastases remained an independent predictor for survival compared with IHC-negative patients (hazard ratio 1.40, 95% confidence interval 1.28–1.53), whereas isolated tumor cells were not a significant predictor (hazard ratio 1.05, 95% confidence interval 0.92–1.20).*
Conclusion. *Patients with occult micrometastases in axillary lymph nodes found via IHC demonstrated a significant overall survival difference, but isolated tumor cells have no prognostic significance. (Surgery 2015;158:494-500.)*

From the The Hiram C. Polk, Jr. MD, Department of Surgery, University of Louisville School of Medicine, Louisville, KY

In 2014, there were an estimated 232,670 new cases of invasive breast cancer, with approximately 40,000 deaths. Although most patients will have localized disease at the time of diagnosis, up to 40% will present with regional or distant spread.[1] Given that metastasis to the regional lymph nodes is the most important prognostic factor in early invasive breast cancer, accurate staging of the lymph nodes is critical.[2] As early as 1948, it was recognized that limited pathologic sampling of lymph node sections was not adequate to identify all metastatic foci, and occult disease deposits remained undetected.[3] Over the years, multiple new techniques have been introduced to improve the detection of nodal disease. A major advance occurred with the introduction of sentinel lymph node biopsy. Because fewer lymph nodes are removed than with axillary dissection, a more comprehensive pathologic examination with serial sectioning of lymph nodes can be performed.[4] The addition of immunohistochemistry (IHC) may identify occult disease in up to 20–25% of cases.[5] The finding of occult disease often represents micrometastatic tumor deposits (<2 mm), including isolated tumor cells.

The interpretation of occult micrometastases has been controversial. Although the authors of several previous studies indicate the degree of micrometastatic tumor burden impacts overall or disease-free survival, others argue that micrometastases have no prognostic value.[6-15] The heterogeneous application of different pathologic methodologies (including the use of IHC)

Presented at the 10th Annual Academic Surgical Congress in Las Vegas, NV, February 3–5, 2015.

Accepted for publication March 18, 2015.

Reprint requests: Nicolas Ajkay, MD, Division of Surgical Oncology, The Hiram C. Polk, Jr. MD, Department of Surgery, University of Louisville School of Medicine, Louisville, KY 40292. E-mail: nicolas.ajkay@louisville.edu.

0039-6060/$ - see front matter

http://dx.doi.org/10.1016/j.surg.2015.03.049

complicates the interpretation of these studies.[12] Furthermore, there are varying definitions of occult disease; whereas some studies separate micrometastatic foci from isolated tumor cells, others combine these populations into one occult disease group. The American Joint Committee on Cancer introduced different classifications for (1) isolated tumor cells (<0.2 mm or 200 individual cells) and (2) micrometastases (between 0.2 and 2.0 mm in size) into the 6th edition of their staging manual, largely over doubts that isolated tumor cells had any prognostic significance.[16] Under this classification, which was continued into the more recent 7th edition of the American Joint Committee on Cancer staging manual, isolated tumor cells are considered lymph node-negative [N0(i+)], whereas micrometastases are defined as lymph node-positive (N1mi).

The controversy over occult metastases is complicated further by debates concerning the role of IHC. Both a recent, randomized controlled trial and a large prospective observational study have explored the issue. Results from the National Surgical Adjuvant Breast and Bowel Project randomized controlled trial B-32 (NSABP B-32) and the American College of Surgeons Oncology Group (ACOSOG) Z0010 study did not suggest a real benefit to the use of IHC in staging lymph nodes. Although a statistically significant difference in overall survival was seen in NSABP B-32, it was only a difference of 1.2 percentage points at 5 years and, thus, of little clinical relevance.[17] The ACOSOG Z0010 study failed to demonstrate any survival advantage associated with IHC; patients with occult metastases identified by IHC had a 5-year survival of 95.1%, compared with 95.7% for those with negative lymph nodes ($P = .64$).[18] As a result of these findings, the authors of both studies questioned the routine use of IHC to stage lymph nodes. Current guidelines for breast cancer staging do not recommend routine use of IHC for clinical decision making.[19]

In this study, we used the Surveillance, Epidemiology, and End Results (SEER) database to compare overall survival among patients with occult nodal metastasis identified by IHC. By using SEER, we sought to evaluate the use of IHC to stage lymph nodes outside of clinical trials or observational studies by using a large patient cohort representative of the general population and reflective of general practice patterns. Our underlying hypothesis was that for patients found initially to be node-negative on routine pathology, subsequent staging information obtained via IHC does not yield any significant, clinically important prognostic information regarding overall survival.

METHODS

Dataset. The SEER database was queried for all cases of invasive breast cancer between 2004 and 2011, excluding patients with evidence of metastatic disease. Using the common schema breast site codes, we then restricted the dataset to patients who had regional lymph nodes that were negative on hematoxylin and eosin staining (H&E) but also were evaluated with IHC.[20] Classification of nodal status on IHC included: N0(i−), indicating IHC-negative for tumor; N0(i+), indicating IHC-positive for isolated tumor cells (<0.2 mm or less than 200 individual cells); or N1mi, indicating IHC-positive for micrometastatic disease (0.2–2 mm in size). Also included in the dataset were covariates reflecting patient demographics (age, sex, race), tumor histology and pathology (T-stage, grade, hormone receptor status, histology), use of adjuvant radiation, vital status, and survival time. HER-2 receptor status was not recorded within SEER for all years of the study and was only available for less than one-third of the patients ($n = 28{,}303$).

Statistical analysis. All statistical analysis was performed using SAS version 9.4 (Cary, NC). Initial data exploration included descriptive statistics for each covariate stratified by N-stage. For continuous variables, means were compared across each group using analysis of variance, whereas categorical variables were compared using a χ^2 test. Overall survival was assessed using the Kaplan-Meier product-limit method. Yearly estimates of survival for each strata of N-stage were taken from the accompanying life table. The log-rank test was used to test for a significant difference in the number of deaths across the three N-stage levels. In addition to stratification by N-stage, survival analysis also was performed with N0(i+) and N1mi patients pooled into an occult disease group to help make our results comparable with studies such as the ACOSOG study Z0010 that did not discriminate between isolated tumor cells and micrometastatic disease.

A Cox-proportional hazards model was then run to control for the effects of all covariates on the event of death. The model included variables found to be significant on univariate analysis, as well any pertinent variables known from the breast cancer literature to be predictive of survival. Observations with missing data for any covariate