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Original contribution

Factors associated with residual disease after initial breast-conserving surgery for ductal carcinoma in situ ☆

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Summary Breast-conserving surgery with radiation therapy has become a standard treatment option in women with localized ductal carcinoma in situ. Re-excision is common in breast-conserving surgery, partly due to lack of consensus on what might constitute an adequate margin. In this study, we aimed to identify potential predictive factors for presence/absence of residual disease after initial breast-conserving surgery. Of 232 cases with a diagnosis of ductal carcinoma in situ without invasive carcinoma at initial biopsy between 2005 and 2009, 108 patients underwent breast-conserving surgery, of which 46 had re-excisions due to close margins (≤2 mm). The notable features significantly associated with ductal carcinoma in situ residuum (19/46; 41%) on univariate logistic regression analysis included the number of close margins, the percentage of sections with ductal carcinoma in situ, and the number of duct spaces with ductal carcinoma in situ (no. of ductal carcinoma in situ ducts) at close margins. Only the percentage of sections with ductal carcinoma in situ remained a significant factor associated with outcomes on multivariate analysis, whereas the number of ductal carcinoma in situ ducts at close margins held borderline predictive value ($P = .054$). Furthermore, logistic regression and classification and regression tree analysis using the 10-fold cross validation method revealed optimal predicting accuracy by using the 3 significant factors in univariate analysis. The final decision tree was constructed by using the number of ductal carcinoma in situ ducts at close margins and the percentage of sections with ductal carcinoma in situ. Thus, these 2 factors represent the most powerful predictors for residual disease on re-excision. Optimal discriminatory power for prediction of absence of residual disease was achieved with cutoffs of 18 ductal carcinoma in situ ducts at close margins and 51.3% sections with ductal carcinoma in situ.

1. Introduction

Ductal carcinoma in situ (DCIS) is a noninvasive, intraductal epithelial proliferation with an inherent but not necessarily obligate tendency for progression to invasive breast carcinoma. It encompasses a wide spectrum of disease

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ranging from low-grade lesions to high-grade lesions that are more likely to be associated with invasive carcinoma. Comprehensive mammographic screening and technological advances in imaging techniques have resulted in increased detection of DCIS, which now accounts for approximately 20% of newly diagnosed breast carcinomas [1]. Among many management paradigms for DCIS, breast-conserving surgery (BCS) with radiation therapy is now a standard treatment option in women with localized DCIS, with high rates of local control and low rates of disease-specific mortality [2].

The most important factor influencing the possibility of recurrence is persistence of neoplastic cells postexcision. In this context, margin status has been considered a major risk factor for residual disease and local recurrence. Consequently, re-excision is common in BCS, although consensus on what constitutes an adequate margin is lacking [3-6]. Recent meta-analyses have shown that a margin threshold of 2 mm appears to be as good as a larger margin when BCS is combined with radiation [2].

Previous studies have shown that recurrence rates for DCIS might also be associated with younger patient age, symptomatic presentation, multifocality, nuclear grade, histologic type, comedonecrosis, tumor size, the volume of tumor in the specimen and near the margin, and hormonal receptor expression profiles [4,6-13]. However, all of these factors have been linked to long-term recurrence, and the clinical and pathologic factors associated with residual occult disease immediately after BCS for DCIS, which have more proximate impact on surgical management, have not been well established. Thus, in this study, we aimed to identify potential predictive factors for the presence/absence of residual disease after initial BCS for DCIS.

2. Materials and methods

After approval by the University of Alabama at Birmingham Institutional Review Board, review of the surgical pathology database of the authors' institution was performed to identify cases with a diagnosis of DCIS at initial needle core biopsies between January 2005 and December 2009. Those with DCIS only and with subsequent BCS were reviewed. Re-excision for margins 2 mm or less was performed per institutional policy, with final treatment decisions based on physician and patient discretion.

All BCS specimens were oriented with marking sutures or by appropriate ink on their external surfaces in the operating room. Specimens were serially sectioned and entirely submitted in 80% of the cases. Perpendicular sections were obtained where the tumor approached the margins to allow microscopic measurement of distance of DCIS from the surgical margin. In the remaining 20% of cases where there were solitary lesions and abundant adjacent normal-appearing breast parenchyma, the lesions were submitted in toto, and the apparent normal breast tissue was representatively submitted with respective margins. Specimen radiographs were accompanied in all cases. The patients' demographic data were retrieved from our institution's electronic database.

All slides of cases requiring re-excision were rereviewed by 2 authors (S. W. and C. K.). The following clinical and pathologic parameters were recorded from the initial biopsy and subsequent BCS specimens: patient age at diagnosis; DCIS characteristics including the highest nuclear grade, histologic type (pattern), necrosis, microcalcifications, and hormonal receptor status; specimen margin status (negative, $\leq$2 mm or tumor touching ink); the percentage of sections (abbreviated as % sections in the tables) with DCIS (calculated against the total number of sections examined, including sections of adjacent benign breast tissue); the number of duct spaces with DCIS (or terminal duct lobular units with cancerization of lobules, abbreviated as no. of DCIS ducts) at close margins (tumor touching ink or $\leq$2 mm in all margin sections), as illustrated in Fig. 1; and whether the specimen was submitted partially or entirely for histologic examination. Overall, the interobserver agreement was greater than 90%. In cases of discordance, the sections were rereviewed to reach the consensus.

The likelihood of having residual DCIS was estimated by univariate and multivariate analysis using logistic regression models [14]. $P = .05$ was considered statistically significant.

Assessment of outcomes (presence/absence of residual tumor in re-excision) was performed by logistic regression analysis using the 10-fold cross validation model. Specifically, 41 samples were randomly chosen as the training set to construct the logistic regression model, and the remaining 5 samples were used as the test set. This procedure was repeated 10 000 times, and the average prediction accuracy was recorded. Similarly, outcome prediction was also carried out by classification and regression tree (CART) analysis [15] implementing the 10-fold cross validation model. The decision tree was constructed using all 46 samples and slightly modified because of model overfitting.

The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy for outcome prediction in models with different cutoffs were determined using 2 thresholds as follows:

1. If the number of DCIS ducts at close margins is less than threshold A:
   a. If the percentage of sections with DCIS is less than threshold B, the outcome is 0 (residual tumor absent).
   b. If the percentage sections with DCIS is greater than threshold B, the outcome is 1 (residual tumor present).
2. If the number of DCIS ducts at close margins is greater than threshold A, the outcome is 1.

Statistical analysis was performed by using the statistical computing software R, available from the Comprehensive R Archive Network at http://www.r-project.org.