Pathologic Variables Predictive of Breast Events in Patients With Ductal Carcinoma In Situ

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Abstract

Central pathology review of ductal carcinoma in situ from 1,456 patients enrolled in National Surgical Adjuvant Breast and Bowel Project (NSABP) protocol B-24 was performed to determine predictors for ipsilateral breast tumor recurrences and contralateral breast cancers. Findings after a median follow-up time of 10.5 years revealed ductal comedo necrosis, micropapillary histologic tumor type, and multifocality to be independent high risk factors for ipsilateral breast tumor recurrence. Risk increased for slight comedo necrosis vs absent and for moderate to marked comedo necrosis vs slight. The presence of a micropapillary tumor type and gross tumor size (≥1.0 cm) were independently found as risk factors for contralateral breast cancers. Although 47% of ipsilateral and 66% of contralateral events were invasive carcinomas, overall mortality was only 2.3%, a conundrum possibly related to the small size of the latter. The similar predictive role of comedo necrosis in this study and that reported previously from NSABP B-17 (total of 2,079 patients) strongly supports its role as a simple high-risk predictor for ipsilateral breast tumor recurrences.

In 1993 and 1998, the National Surgical Adjuvant Breast and Bowel Project (NSABP) published the 5- and 8-year results of its B-17 trial,1,2 which had been designed to examine the natural history and treatment of ductal carcinoma in situ (DCIS). Results showed that the administration of local breast irradiation (XRT) following local excision with removal of sufficient breast tissue to provide free margins (LE) significantly reduced the frequency of ipsilateral breast tumor recurrences (IBTRs). The 12-year results of the study3 showed that IBTR was reduced by 57% (rate ratio [RR] = 0.43), 62% (RR = 0.38) for invasive and 51% (RR = 0.49) for noninvasive IBTR. A centralized pathology review of specimens and reports from 623 of the 814 patients enrolled in the B-17 trial revealed that tumors with moderate to marked comedo necrosis and involved margins were independent predictors for IBTR at 5 years.4 Only the former has been found to be significant in this regard at 8 years.5

Although the B-17 trial included only women whose DCIS appeared to be localized, it was becoming evident that women with involved margins or with DCIS accompanied by multiple calcifications that may have been other DCIS were often treated by mastectomy. At about this same time, the antitumor properties of tamoxifen were becoming apparent. These considerations led to NSABP trial B-24 in 1991 to assess the effectiveness of XRT with or without tamoxifen following LE to determine whether this adjuvant hormonal therapy might allow for breast conservation in women with DCIS. The 5-year results from that trial including nearly 1,800 women revealed that IBTR was reduced approximately 30% (RR = 0.70) in women who received tamoxifen after postoperative XRT compared with women who received only postoperative XRT.6 This reduction was most pronounced in...
the IBTR that was invasive. These findings continued through 7 years of follow-up.³

Because there has been no consensus about the classification and identification of risk factors for outcomes in DCIS, we considered it worthwhile to review the pathology materials from protocol B-24 to determine what variables might be related to subsequent breast events.

Materials and Methods

The details of patient eligibility and treatment of women who participated in NSABP trial B-24 have been reported previously.³,⁶ All who participated provided written consent before random assignment to one of the treatment groups.

Trial B-24 included 1,799 women, 899 of whom had been randomly assigned to LE, XRT, and tamoxifen (20 mg daily for 5 years) and 900 of whom had been assigned to LE, XRT, and placebo. Central review of pathology material revealed that 1,456 cases (80.9% of the total cohort) were acceptable for further analyses. The median time in the study for this subset of patients was 10.5 years.

Table 1 lists 10 pathologic characteristics examined (described in detail previously⁴,⁵,⁷-¹⁰). For the purposes of this study, the description multifocal indicates the presence of DCIS in sections prepared from more than 1 different block of a specimen within the same quadrant as the index lesion. Tumor in only 1 of several different blocks was regarded as unifocal. If only 1 block of tumor was available, focality was indicated as unknown. Our definition of multifocality was adopted in the past because standard dictionaries failed to provide a clear distinction between it and multicentricity. Multicentricity in our studies has been used to designate lesions in multiple quadrants as opposed to those that were multiple in the same quadrant.

We assessed comedo necrosis as an independent feature rather than as representative of a specific histologic tumor type and graded it as slight when it appeared in fewer than one third...
of tumor ducts and moderate to marked when in more than one third. This was a departure from the groupings used in protocol B-17 in which the slight and absent categorizations were grouped and analyzed together. Microscopically, margins of resection were considered free when tumor was not transected by ink. The degree of this freedom was assessed as less than 1.0 mm or 1.0 mm or more (Table 1). A transected margin in a noninked specimen was designated uncertain when one could not be sure if it represented a tumor margin or patient surface. Nuclear grade was assessed as good or poor, the former representing conventional grades 1 and 2 and the latter, grade 3. It should be emphasized that the histologic tumor types were not quantitatively estimated but were considered as being present when identified in a particular tumor alone or with other types.

Gross tumor size was obtained from the reports provided to the NSABP by pathologists from the various institutions participating in the study. For our purposes, any measurements stated as fractions less than 1.0 cm (eg, 0.9 cm or 0.8 cm) were entered as less than 1.0 cm. Microscopic size was represented as the greatest dimension found in any slide and included nontumorous intervening tissue when several foci of an in situ lesion were encountered in the same section. This mimicked the method of macroscopic tumor measurement. Last, the degrees of tumor stroma and lymphoid infiltrate were subjectively graded.

Because we did not receive pathology sections from the IBTRs or contralateral breast cancers for central review, the decision about whether these were invasive or noninvasive or both was based on careful review of institutional pathology reports.

We used $\chi^2$ tests to compare selected patient characteristics (ie, age, race, treatment assignment, outcomes, and follow-up time) of the subset of 1,456 patients with adequate pathology material available with those of the remaining 343 patients of the clinical cohort. We made these comparisons to determine the commonality of characteristics between the pathologic subset and the remaining B-24 population. Log-rank tests were performed to compare follow-up time and disease-free survival in these 2 populations.\(^{11}\) Differences in the rates of IBTR and treatment effects between the pathologic subset and the remaining B-24 population were tested by Cox proportional hazards modeling.

Frequency distributions for the pathologic features in the subset of 1,456 patients were compared by treatment groups using $\chi^2$ tests of homogeneity. Average annual IBTR rates according to pathologic features were computed as ratios of the number of events to total person years of observation.\(^{12}\)

The Cox proportional hazards model was used to further evaluate the prognostic significance of each pathologic feature in relation to risk of IBTR.\(^{13,14}\) Variables associated with IBTR at an $\alpha$ of .10 or less in bivariate analyses were evaluated jointly in a multivariate analysis to determine which were independently associated with the risk of IBTR. The cumulative incidence of IBTR was computed taking into account competing risks.\(^{15}\) Analogous Cox regression modeling and cumulative incidence calculations were performed for contralateral breast cancers.

**Results**

Distributions by age, race, treatment assignment, IBTR, disease-free survival, and follow-up time were comparable in the subset of patients for whom pathology material was available (1,456) and the remainder of the cohort (343). Inexplicably, more tumors were detected mammographically ($P = .008$) and were grossly smaller ($P = .007$) in the subset. There were no significant differences in the distributions of the pathologic variables between the 2 treatment arms.

Of the 734 patients of the original 900 enrolled in the placebo arm for whom pathology material was available, 109 (14.9%; 17.4 events per 1,000 patient years) exhibited an IBTR. Of these, 54 (49.5%) were invasive carcinomas. Of the 722 in the eligible tamoxifen-treated group, 80 (11.1%; 12.2 events per 1,000 patient years) had IBTRs, and 35 (43.8%) of these were invasive. The average annual rates and RR of these events according to pathologic variables and treatment are shown in Table 1. Bivariate Cox regression analysis for IBTR (including the pathologic variable and treatment) revealed moderate to marked lobular cancerization, microscopic ($<0.5$ cm and $\geq$0.5 cm) and gross ($<1.0$ cm and $\geq$1.0 cm) tumor size, poor nuclear grade, moderate to marked stromal response, moderate to marked and slight comedo necrosis (vs absent), multifocality, involved margins, and low papillary histologic tumor type to be significantly ($P < .05$) related to such an event. The risks for IBTR appeared to be reduced by tamoxifen for all pathologic variables except when comedo necrosis was absent (Figure 1) or a tumor was small microscopically (on 03/12/2019).

Significant for predicting IBTR in multivariate analysis were the presence of micropapillary histologic tumor type, moderate to marked and slight comedo necrosis compared with its absence, and multifocality. Moderate to marked comedo necrosis exhibited a greater risk than when this change was graded as being slight ($P = .037$). Status of margins was not significant for predicting IBTR.

The margins of excision of all index lesions that were found to be free revealed the degree of this freedom to be less than 1.0 mm in 45.4% and 1.0 mm or more in 24.2%. Margins were uncertain in 16.1% and involved in 14.3%.

There were 40 (5.4%) contralateral breast cancers in the placebo arm and 33 (4.5%) in patients treated with tamoxifen. Of the 40 contralateral breast cancers in the placebo group, 27 (68%) were invasive, and 21 (64%) were invasive in the
Significant bivariate predictors for contralateral breast cancer were presence of micropapillary histologic tumor type and moderate to marked comedo necrosis. The former predictor was also significant by multivariate analysis. Moderate to marked comedo necrosis was marginally so ($P = .051$).

The average size of all new invasive breast cancers was 1.0 cm. Of 71 invasive IBTRs with size information available, 34 (48%) were smaller than 1.0 cm. Of the 40 invasive contralateral breast cancers with size information available, 16 (40%) were smaller than 1.0 cm. Table 2 indicates the very low frequency (2.3%) of total deaths attributable to breast cancer in the pathologic subset and their relationship with or without prior IBTR or contralateral breast cancer of invasive or noninvasive type and regional and distant disease.

### Discussion

The independent pathologic variables found to be prognostic for IBTR in this study are in large part comparable to those observed previously in NSABP protocol B-17, a clinical trial that revealed a significant reduction of IBTR by local

### Table 2

<table>
<thead>
<tr>
<th>Category of Death Due to Breast Cancer</th>
<th>Placebo (n = 734)</th>
<th>Tamoxifen (n = 722)</th>
<th>Total No. (%) (N = 1,456)</th>
<th>Breast Cancer to Death (y)</th>
<th>Registration to Death (y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>With prior IBTR (n = 14)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive*</td>
<td>7</td>
<td>3</td>
<td>10 (0.7)</td>
<td>3.0 (1.0-5.8)</td>
<td>75 (2.0-9.9)</td>
</tr>
<tr>
<td>Noninvasive</td>
<td>0</td>
<td>4</td>
<td>4 (0.3)</td>
<td>2.6 (2.6-6.8)</td>
<td>5.2 (4.3-9.5)</td>
</tr>
<tr>
<td>With prior contralateral breast cancer (n = 10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive*</td>
<td>5</td>
<td>4</td>
<td>9 (0.6)</td>
<td>4.5 (0.3-7.0)</td>
<td>8.1 (6.1-11.6)</td>
</tr>
<tr>
<td>Noninvasive</td>
<td>0</td>
<td>1</td>
<td>1 (0.1)</td>
<td>2.8</td>
<td>4.5</td>
</tr>
<tr>
<td>Prior regional or distant breast cancer* (n = 9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive*</td>
<td>6</td>
<td>3</td>
<td>9 (0.6)</td>
<td>0.7 (0.4-8.0)</td>
<td>6.2 (3.0-9.7)</td>
</tr>
<tr>
<td>Noninvasive</td>
<td>0</td>
<td>1</td>
<td>1 (0.1)</td>
<td>2.8</td>
<td>4.5</td>
</tr>
<tr>
<td>Total</td>
<td>18</td>
<td>15</td>
<td>33 (2.3)</td>
<td>2.8 (0.7-5.0)</td>
<td>7.5 (2.0-11.6)</td>
</tr>
</tbody>
</table>

IBTR, ipsilateral breast tumor recurrence; NSABP, National Surgical Adjuvant Breast and Bowel Project.

* Includes pure invasive and pure invasive mixed with ductal carcinoma in situ.

† Regional includes tumors in axillary soft tissue or that are infraclavicular, axillary, or supraclavicular and ipsilateral internal mammary nodes, chest wall; distant includes bone marrow, lung, liver, central nervous system, and cutaneous.
XRT following LE of DCIS. The increasing risk of IBTR according to degrees of comedo necrosis in the present study indicates that this characteristic is an important risk factor. It further enhances previous B-17 findings because the group labeled slight was included with the group labeled absent in those analyses. Thus, after appropriate controls for treatment, comedo necrosis has been found to be a consistent, independent predictor for IBTR for a combined 2,079 patients (B-17, 623 + B-24, 1,456) with DCIS. The B-17 data indicated that the solid, but not the micropapillary, histologic type, as in the present study, is an independent discriminant for IBTR, although both tumor types were shown to be significant by univariate analysis in trial B-17. It should be noted that our findings are different from those recently reported by others who failed to observe comedo necrosis as an important risk factor for IBTR. We suggest that the retrospective nature, small numbers of patients (132 compared with 1,456), and differences in definition of features examined may have had a role in this dichotomy.

The relationship of the status of margins following LE of DCIS to IBTR, particularly the definition of what is free, continues to be controversial. NSABP pathologic practice regards the boundary of a tumor to be free if sections do not reveal its transection by ink. Estimates of being too close, at, or near are considered vague and conjectural. Indeed, the extent of a free margin that may be necessary to reduce IBTR following lumpectomy has not been inarguably demonstrated and, if excessive, may preclude satisfactory cosmesis, the fundamental purpose of that type of conservative surgical treatment. Involved margins in the B-17 trial represented an independent risk factor for IBTR at 5 years but not 8 years of follow-up, a finding that coincides with those in this report after 10.5 years of observation. Our data reveal that the degree of freedom of margins was almost twice as frequently less than 1.0 mm than it was 1.0 mm or more, an observation that coincides with the senior author’s impression in consultative practice. This may reflect an intraoperative difficulty in assessing the freedom of margins for very small, impalpable lesions that cannot be seen or felt despite the presence of a guide wire. It is noteworthy that the frequency of IBTR recorded in trial B-17 and in the trial B-24 placebo group does not exceed that noted in several reviews of retrospective studies. We maintain that margins should be free of disease, although when breast conservation is desired, as in trial B-24, margin status may not be necessary provided tamoxifen is administered as an adjuvant to XRT.

Information about the possible predictors of risk for the development of contralateral breast cancer in patients with DCIS has been lacking. In the B-17 trial, there were relatively small numbers of such events in that pathologic subset, which precluded such analysis at that time. However, in the present study, multivariate analysis disclosed that the presence of low papillary histologic tumor type was significantly related to this event. Comedo necrosis was marginally related. The precise biologic implications of these associations are unclear, although they may indirectly reflect a predilection for bilaterality in DCIS.

The mortality data we observed in this subset of patients was similar to that observed in patients with DCIS in protocol B-17 and represents one of the interesting and challenging conundrums of DCIS. Much attention continues to be directed to the reduction of invasive IBTR and contralateral breast cancer in DCIS. Although the percentages of IBTR and contralateral breast cancer that were invasive cancers in our study were 47% and 66%, respectively, the combined mortality due to breast cancer at 10.5 years was only 2.3% of the total pathologic subset. This outcome was similarly low in B-17 (1.6%) at 8 years of follow-up. One explanation for this unexpectedly low mortality might be related to the small size of the invasive cancers of IBTR for which we have data, 1.0 cm in the present study and 1.3 cm in the B-17 trial. It does not seem to be the result of an inadequate period of observation following IBTR and contralateral breast cancers because these times were not short. We have no explanation for the discrepancy in mortality, which was approximately less than twice that in the European Organisation for Research and Treatment of Cancer phase 3 trial at a follow-up period similar to that in this study. It should also be noted that the former report was based on intent-to-treat data and lacked important pathologic details relating to what was well-, intermediate-, and poorly differentiated DCIS. Apparently, no other characteristics were examined.

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