Impact of Estrogen Receptor Expression and Other Clinicopathologic Features on Tamoxifen Use in Ductal Carcinoma In Situ

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BACKGROUND. Recent data have demonstrated that benefit from adjuvant tamoxifen therapy for patients with ductal carcinoma in situ (DCIS) is limited to estrogen receptor (ER)-positive lesions. The objective of the current study was to correlate clinicopathologic features of DCIS with ER expression and the impact of this information on tamoxifen counseling.

METHODS. Women with DCIS who were treated from 2001 to 2004 were evaluated. Routine ER staining was initiated in January 2003.

RESULTS. Ninety-four women (mean age, 57.6 years) were analyzed. The mean DCIS size was 0.98 cm. ER-staining was performed in 55 lesions, and 76% were ER-positive. All Grade 1 and 2 DCIS lesions were ER-positive, compared with 54% of high-grade lesions ($P<.001$); no other clinicopathologic feature significantly predicted ER status. Overall, 58 patients (62%) were offered tamoxifen, and the rates were similar for the pre-ER and post-ER staining periods. In the pre-ER staining period, surgical treatment and grade were associated with offering tamoxifen (75% of patients who underwent breast conservation vs. 40% of patients who underwent mastectomy; $P = .03$; 78% of patients with Grade 1 or 2 lesions vs. 45% of patients with Grade 3 lesions; $P = .04$). In the post-ER staining period, however, only ER status was correlated significantly with offering tamoxifen (71% of patients with ER-positive lesions vs. 31% of patients with ER-negative lesions; $P = .01$). Approximately 66% of patients who were offered tamoxifen agreed to treatment (approximately 33% of the total DCIS study sample). No clinicopathologic features predicted for tamoxifen acceptance by patients in either the pre-ER or post-ER staining periods.

CONCLUSIONS. Seventy-five percent of DCIS lesions were ER-positive. ER staining significantly influenced the likelihood that clinicians would offer tamoxifen to patients with DCIS, but it had no impact on whether patients accepted treatment.
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KEYWORDS: ductal carcinoma in situ, tamoxifen, chemoprevention, estrogen receptor positive.

The routine use of screening mammography has resulted in a dramatic increase in the diagnosis of ductal carcinoma in situ (DCIS), which now represents >20% of all screen-detected breast cancers in North America, and >50,000 women are newly diagnosed with DCIS in the United States each year.[1,2] Because the volume of patients with DCIS has grown, insights into the heterogeneity of this disease has deepened, and this has resulted in controversy regarding the optimal management for these lesions.[3]

The noninvasive nature of DCIS (defined as absence of invasion beyond the basement membrane) is the basis for its primary man-

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agement predicated on local therapeutic strategies, including mastectomy, lumpectomy, and radiation therapy. These approaches are very effective as definitive management, yielding long-term overall survival in ≥97% ofpatients[4–7] A personal history of DCIS, however, leaves patients at high risk for developing subsequent invasive and noninvasive breast cancers in both the affected breast and the unaffected breast. Furthermore, among patients with DCIS who are managed by breast-conserving approaches, approximately 50% of all local recurrences will have an invasive histology.[6–10] These patterns underscore the importance of properly selecting local therapy so that morbidity and mortality risks from an invasive recurrence can be minimized; they also have motivated studies of chemoprevention agents (e.g. tamoxifen and aromatase inhibitors) as adjuvant therapy for DCIS.[11,12]

The National Surgical Adjuvant Breast Project (NSABP) B-24 trial demonstrated that the addition of tamoxifen to lumpectomy for DCIS resulted in lower incidences of subsequent invasive and noninvasive breast cancer events in both the affected breast and the contralateral breast.[11] Thus, tamoxifen was an effective chemopreventative agent for patients with DCIS. The potential for adverse effects from tamoxifen therapy has resulted in a relatively low rate of tamoxifen acceptance among patients with DCIS,[13,14] suggesting the need for better stratification of patients with DCIS who require adjuvant therapy. To address this need, a retrospective analysis of the B-24 trial was conducted by Allred et al.[15] with estrogen receptor (ER) staining in DCIS lesions; their study revealed that the benefit from tamoxifen therapy was limited to patients with ER-positive DCIS. The findings of Allred et al. have been powerful enough to result in the initiation of routine staining for ER expression in DCIS lesions at many institutions. Furthermore, ER-positive status is a primary eligibility criterion for the current NSABP study of DCIS (B-32), which randomizes postmenopausal women who undergo lumpectomy and radiation to receive either tamoxifen or anastrozole.[12]

The study by Allred et al. and their findings regarding ER expression in DCIS have had a substantial impact on pathology specimen handling and on cooperative group clinical trial eligibility. ER staining is employed routinely for invasive breast carcinoma, but this technology is a relatively recent addition to the study and reporting patterns for DCIS. Our objectives were to evaluate clinicopathologic features of DCIS associated with positive ER status and to analyze the extent to which practice patterns regarding adjuvant tamoxifen recommendations are influenced by ER expression compared with other conventionally accepted features of the disease among patients who were treated at a comprehensive breast care center.

MATERIALS AND METHODS

A retrospective, Institutional Review Board-approved chart review of patients with unilateral DCIS who were treated at the University of Michigan Comprehensive Cancer Center from 2001 to 2004 was undertaken. The primary management of DCIS included lumpectomy, lumpectomy plus radiation, or mastectomy. According to commonly accepted practice recommendations, patients with DCIS who underwent mastectomy had concomitant axillary staging by sentinel lymph node biopsy.[16,17] Analysis of the following characteristics was performed: family history, menopausal status, age at menopause, hormone-replacement therapy, oral contraceptive use, method of cancer detection, findings on mammogram, type of biopsy, size of tumor, grade of DCIS, presence of necrosis, ER status, progesterone receptor status, surgical treatment, sentinel lymph node biopsy, tamoxifen offered, and tamoxifen accepted.

Staining for ER was incorporated routinely into the pathology processing of DCIS lesions in January 2003. In brief, our staining procedure for ERs involves the use of an automated stainer (the Ventana Benchmark). Automated antigen retrieval is performed first directly on the stainer to expose the antigenic sites of the paraffin tissue. We then use a Ventana Basic diaminobenzidine detection kit, which uses a standard avidin-biotin peroxidase detection method. After staining is complete, Chromovision image-analysis software is used according to the manufacture's recommendations to quantify the percentage of cells that are stained positive. ER status and progesterone receptor status were considered positive if ≥5% of cells were stained positive.

Chi-square tests were applied for statistical comparisons between categorical variables. The Student *t* test was used for continuous variables. All statistical evaluations were performed using the Statistica software package (StatSoft 2000; Tulsa, OK).

RESULTS

In total, 94 patients were treated for DCIS lesions at the University of Michigan between 2001 and 2004, and had data available for analysis. The clinicopathologic features of our patient population are summarized in Table 1. The mean age was 57.6 years (range, 30-82 years) and most patients (69%) were postmenopausal. The mean DCIS size was 0.98 cm (range, 0.10-5.0 cm). Presenting features of the DCIS included new or changing microcalcifications alone or in combination with a new density in 85% of patients. Approxi-

TABLE 1
Clinicopathologic Features of the Study Patient Population*

Feature	No. of Patients (%)
Estrogen receptor status	
Positive	42 (44.7)
Negative	13 (13.8)
Unknown	39 (41.5)
Mean age [range], y	57.6 [30–82]
Mean DCIS size [range], cm	0.98 [0.1–5.0]
Treatment	
Lumpectomy	12 (12.8)
Lumpectomy and XRT	55 (58.5)
Mastectomy	27 (28.7)
Family history, first-degree relative	
0	74 (78.7)
1	18 (19.1)
≥2	2 (2.1)
Menopausal status	
Premenopausal	28 (29.8)
Postmenopausal	65 (69.1)
Unknown	1 (1.1)
Hormone-replacement therapy	
Yes	40 (42.6)
No	52 (55.3)
Unknown	2 (2.1)
Method of detection	
Mammogram	82 (87.2)
Ultrasound	0 (0.0)
Physical exam	11 (11.7)
Combination	1 (1.1)
Mammographic finding	
Calcification	71 (75.5)
Density	10 (10.6)
Calcification/Density	9 (9.6)
None	4 (4.3)
Method of biopsy	
Wire localization	30 (31.9)
Excisional	7 (7.4)
Stereotactic core needle	51 (54.3)
Ultrasound-guided core needle	1 (1.1)
Freehand core	5 (5.3)
Grade	
Low (Grade 1)	13 (13.8)
Intermediate (Grade 2)	32 (34.0)
High (Grade 3)	49 (52.1)
Necrosis	
Yes	67 (71.3)
No	27 (28.7)
Total	94 (100)

ER: estrogen receptor; DCIS: ductal carcinoma in situ; XRT: radiation therapy.
* Subtotals do not add to 100% in categories of missing or overlapping results.

TABLE 2
Clinicopathologic Features Associated with Positive Estrogen Receptor Status (N = 55 Women with Ductal Carcinoma in Situ)

Feature	No. of ER-Positive Patients (%)	*P*
Grade		
1 or 2	27/27 (100)	
3	15/28 (54)	<.001
History of HRT		
Yes	25/30 (83)	
No	16/24 (67)	.31
History of OCP use		
Yes	25/32 (78)	
No	16/22 (73)	.77
Age, y		
<50	18/20 (90)	
≥50	24/35 (69)	.07
Presence of calcifications on mammography		
Yes	35/46 (76)	
No	7/9 (78)	.99
Family history of breast cancer		
Yes	28/33 (85)	
No	9/12 (75)	.08
Local treatment		
Breast conservation	35/43 (81)	
Mastectomy	7/12 (58)	.10
Menopausal status		
Premenopausal	15/17 (88)	
Postmenopausal	20/28 (71)	.59
Tumor size, cm		
<3	30/40 (75)	
≥3	4/4 (100)	.26

ER: estrogen receptor; HRT: hormone-replacement therapy; OCP: oral contraceptive.

mately 50% of lesions were assessed as high-grade. The DCIS was described as unifocal in 45% of patients and multifocal in 55% of patients.

Nearly 75% patients received breast-conservation therapy (59% underwent lumpectomy and received breast irradiation; 13% underwent lumpectomy alone). Sentinel lymph node biopsy was performed in 28% of women who underwent mastectomy.

Thirty-nine patients (41%) were treated during the pre-ER staining period. In the post-ER staining period, ER expression was positive in 42 of 55 patients (76%). Associations between clinicopathologic features and positive ER status are shown in Table 2. The grade of the DCIS lesions was the only feature that predicted positive ER status; all 27 lesions that were not high-grade DCIS (Grade 1 or 2) were positive for ER expression compared with 15 of 28 lesions that were high-grade DCIS (Grade 3; 54%; $P<.001$). Ninety percent of patients younger than age 50 years had ER-positive DCIS versus 69% of patients age 50 years and older, but this difference did not reach statistical significance. A family history of breast cancer was of borderline significance in its association with positive ER status (85% vs. 75% of patients with and without a family history, respectively; $P = .08$).

Only breast preservation ($P = .03$) and low-grade or intermediate-grade DCIS ($P = .04$) correlated with offering tamoxifen in the pre-ER staining period (Ta-

TABLE 3
Comparison of Clinicopathologic Features and *Offering* Tamoxifen in the Periods Before (N = 39) and After (N = 55) Estrogen Receptor Staining

	Tamoxifen Offered: No. of Patients (%)			
Feature	Pre-ER Staining	*P**	Post-ER Staining	*P**
Grade		.04		.21
Low/intermediate	14/18 (78)		19/27 (70)	
High	9/20 (45)		15/28 (54)	
Treatment		.03		.34
Breast conservation	18/24 (75)		28/43 (65)	
Mastectomy	6/15 (40)		6/12 (50)	
Age, y		NS		.13
≥50	19/32 (59)		19/35 (54)	
<50	5/7 (71)		15/20 (75)	
ER status				.01
Positive†	NA		30/42 (71)	
Negative‡	NA		4/13 (31)	
Family history		.14		.053
Positive§	6/7 (86)		11/13 (85)	
Negative‖	18/32 (56)		23/42 (55)	

ER: estrogen receptor; NS: nonsignificant; NA: not available.
* *P* values were calculated by using chi-square analysis.
† Patients with ≥5% of cells stained for ER.
‡ Patients with <5% of cells stained for ER.
§ Patients who had a family history of breast cancer in ≥1 first-degree relative.
‖ Patients with no family history of breast cancer.

TABLE 4
Comparison of Clinicopathologic Features and *Accepting* Tamoxifen in the Periods Before (N = 39) and After (N = 55) Hormone Receptor Staining

	Tamoxifen Accepted: No of Patients (%)			
Feature	Prestaining	*P**	Poststaining	*P**
Grade		.9		.6
Low/intermediate	9/14 (64)		11/19 (58)	
High	6/9 (67)		10/15 (67)	
Treatment		1.0		.51
Breast conservation	12/18 (67)		18/28 (64)	
Mastectomy	4/6 (67)		3/6 (50)	
Age, y		.07		.37
≥50	11/19 (58)		13/19 (68)	
<50	5/5 (100)		8/15 (53)	
ER status				.09
Positive†	NA		17/30 (57)	
Negative‡	NA		4/4 (100)	
Family history				
Positive§	3/6 (50)	.31	7/11 (64)	.87
Negative‖	13/18 (72)		14/23 (61)	

ER: estrogen receptor, NA: not available.
* *P* values were calculated by using chi-square analysis.
† Patients with ≥5% of cells stained for ER.
‡ Patients with <5% of cells stained for ER.
§ Patients who had a family history of breast cancer in ≥1 first-degree relative.
‖ Patients with no family history of breast cancer.

ble 3). There was a nonsignificant trend toward higher rates of tamoxifen recommendations in patients with DCIS who had a positive family history for breast cancer. In contrast, ER status was the only feature associated significantly with a tamoxifen recommendation during the post-ER staining period ($P = .01$). Family history remained of borderline significance. These results are shown in Table 3. There were no significant differences in whether patients were offered tamoxifen according to their menopausal status (79% of premenopausal women were offered tamoxifen vs. 55% postmenopausal women; $P = .33$) or in whether patients accepted tamoxifen (57% of premenopausal women vs. 33% of postmenopausal women; $P = .35$).

Table 4 shows that none of the clinicopathologic features studied were significantly predictive of patients accepting tamoxifen therapy (Table 4). For most categories, between 50% and 66% of patients accepted a recommendation for tamoxifen therapy. Patterns of acceptance were similar for the pre-ER and post-ER-staining periods.

DISCUSSION

The treatment of DCIS has evolved beyond mastectomy during the past 20 years. Breast preservation is now established as a viable and oncologically safe alternative for the treatment of DCIS based on outcomes from prospective clinical trials.[9,11,18–22] The NSABP B-17 trial demonstrated that the addition of radiation therapy after lumpectomy for patients DCIS reduced the incidence of DCIS in the ipsilateral breast from 13.4% to 8.2% ($P = .007$) at 8 years, and the incidence of invasive ipsilateral events was reduced from 13.4% to 3.9% ($P = .0001$).[18] Although Phase III trials have proven the safety of breast preservation for the management of DCIS in terms of overall survival, the risk of local recurrence remains a persistent challenge.

Trials of systemic therapy for invasive breast cancer demonstrating the effectiveness of tamoxifen in contributing to local control as well as contralateral breast cancer risk reduction[23,24] have ushered in an era of adjuvant endocrine therapy for DCIS, primarily as a means of addressing risk of new in-breast events. Current evidence suggests that tamoxifen is effective adjuvant treatment only for ER-positive cancers and only prevents the formation new ER-positive cancers. The Early Breast Cancer Trialists' Collaborative Group overview study published in 1998 examined tamoxifen use in early-stage breast cancer among 37,000 women from 55 different trials.[25] In that overview, tumors

were classified as ER-negative, ER-positive, or ER-unknown. For the women with ER-negative cancers, tamoxifen offered no benefit. However, for women with ER-positive and ER-unknown cancers, tamoxifen use resulted in a significant improvement in 10-year survival irrespective of all other variables. In the NSABP P-1 trial, tamoxifen was used as a chemopreventative agent in women who were deemed to have a high risk for developing breast cancer.[26] In that trial, invasive cancers were reduced by 49%, and noninvasive cancers were reduced by 50%. It is noteworthy that this reduction was observed only in the development of ER-positive cancers. Specifically, tamoxifen decreased the development of ER-positive tumors by 69% but had no significant effect on the development of ER-negative tumors.

A logical progression in study design was to study a course of tamoxifen therapy after treatment of DCIS with lumpectomy and radiation. The NSABP B-24 trial randomized patients to receive either tamoxifen or placebo after they received treatment for their DCIS with lumpectomy and radiation. Women in the tamoxifen arm experienced a significant benefit at 5 years[11]: The overall risk of breast cancer events was reduced from 13.4% to 8.2% ($P = .0009$). Nonetheless, some clinicians have questioned whether this 5% absolute risk reduction justifies the potential morbidity associated with tamoxifen. These adverse risks include an increased incidence of hot flashes, thromboembolic events, and endometrial cancers.[26] The patient with DCIS faces the risk of tamoxifen-related, adverse sequelae with no evidence of impact on overall survival.

A recent study by Yen et al. from The University of Texas M. D. Anderson Cancer Center evaluated the use of tamoxifen by clinicians after publication of the results from NSABP B-24.[13] Those investigators reported that 60% of patients with DCIS were offered tamoxifen therapy. Factors that were associated with tamoxifen use included low-volume disease and breast preservation. Rates of tamoxifen use also differed between clinicians, who demonstrated individual provider-related bias. Nearly 50% of patients who were offered tamoxifen declined because of concerns regarding side effects. Similarly, Nakhlis et al.[14] observed that >25% of patients with DCIS declined a recommendation for tamoxifen therapy. These findings underscore the need for an improved and objective means of identifying patients with DCIS who will derive a net benefit from tamoxifen therapy.

Allred et al. investigated ER expression as a marker for predicting the effectiveness of tamoxifen in the treatment of DCIS.[15] In their study, ER status was determined for 628 patients who had been enrolled in the NSABP B-24 trial. Of these patients, 327 women received placebo, and 301 women received tamoxifen. Receptor status was determined by immunohistochemistry and a review of documentation. The authors found that 77% of the cancers were ER-positive, and 23% were ER-negative. In the ER-positive tumors, Allred et al. observed a 59% reduction in the ipsilateral and contralateral development of new cancers ($P = .0002$). However no benefit was observed for patients who received tamoxifen if their tumor was ER-negative. These data suggest that tamoxifen therapy for patients with DCIS should be restricted to those who have ER-positive lesions.

In the current study we analyzed clinicopathologic features that were associated with ER expression in DCIS and studied the influence of ER staining on practice patterns regarding counseling for tamoxifen therapy. Similar to the data reported by Allred et al., approximately 75% of the DCIS lesions at our comprehensive cancer center were positive for ER staining by immunohistochemistry, and we also observed that high-grade DCIS lesions were less likely to express ER compared with low-grade and intermediate-grade lesions. Prior to routine ER staining, breast-conservation therapy was the primary feature correlated with whether patients were offered tamoxifen. This is consistent with practice patterns reported by others.[13,27] Furthermore, our study confirmed a strong influence of ER staining on adjuvant therapy counseling; and, once routine ER testing was adopted, these results became the primary determinant of tamoxifen recommendations.

It is noteworthy that, according to the current results, features associated with a recommendation to use tamoxifen during the pre-ER staining period (patients who underwent lumpectomy, patients with low-grade or intermediate-grade disease, and patients who had a positive family history for breast cancer) also were correlated with positive ER status during the poststaining period. Patient reluctance regarding tamoxifen therapy, nonetheless has persisted, with 33% of patients ultimately declining tamoxifen therapy regardless of ER-staining results. It should be noted that the relatively small sample size in the current study presents some limitations in the strength of statistical patterns. Additional studies are warranted to address DCIS and ER expression.

In conclusion, decision-making regarding tamoxifen use as adjuvant therapy for women with DCIS remains difficult. Clinicians and patients are concerned about the cost and side effects associated with tamoxifen. In the current study, we chronicled how a comprehensive cancer center revised tamoxifen counseling patterns in the management of DCIS. This

change was in response to recent evidence showing increased benefits of tamoxifen in women with ER-positive DCIS. The rates of tamoxifen refusal nevertheless remain substantial. Therefore, continued efforts to identify objective criteria associated with net benefit from endocrine therapy among patients with DCIS are warranted.

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