REVIEW

Ductal Carcinoma In Situ (DCIS) of the Breast: Perspectives on Biology and Controversies in Current Management

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The incidence of ductal carcinoma in situ (DCIS) has increased because of increasing use of sensitive imaging modalities. MRI is commonly used for the detection of breast cancer but has not yet been validated in randomized trials. There have not been randomized trials addressing optimal margins of excision or axillary sampling. Whole breast radiation after lumpectomy decreases the risk of recurrence but may be omitted in selected patients. Adjuvant Tamoxifen reduces the risk of recurrence but has no impact on overall survival rates. J. Surg. Oncol. 2012;105:212–220. © 2011 Wiley Periodicals, Inc.

KEY WORDS: ductal carcinoma in situ; breast; DCIS

INTRODUCTION

With the implementation of widespread screening mammography in the 1980s and the increasing use of highly sensitive imaging modalities, such as magnetic resonance imaging (MRI), the incidence of ductal carcinoma in situ (DCIS) has increased considerably over the past several decades. Thus, there are pressing questions regarding optimal management. DCIS describes lesions characterized by proliferation of abnormal epithelial cells with an intact basement membrane and no evidence of stromal invasion [1]. While the clinical course of DCIS is quite variable, it is considered a non-obligate precursor to invasive breast cancer. The majority of cases may not progress to an invasive state; however, reliable prognostic and predictive markers to guide treatment remains an unmet need. This article will review the natural history of DCIS and discuss the current therapeutic options and challenges in patient management.

NATURAL HISTORY OF DCIS

The natural history of DCIS is complex, given its heterogeneity. Advanced genomic analysis has identified genetic alterations that correlate with DCIS grade [2]. Losses of chromosomal material at 16q were characteristic of well- to moderately-differentiated DCIS while poorly differentiated DCIS was more likely to have a series of DNA amplifications. These analyses also compared DCIS with adjacent invasive breast cancer cells and confirmed a near-identical genetic pattern between them. Genetic similarities between invasive breast cancer and poorly differentiated DCIS were confirmed in separate, larger studies [3]. These data support the role of DCIS as a precursor to invasive breast cancer, though the events necessary for this transformation remain unclear.

DCIS was relatively rare before 1980, and most historical cases were diagnosed after surgical resection of a suspicious breast mass [4]. As a result, the long-term natural history of DCIS has been poorly described. Insight can be garnered from analysis of patients with DCIS that were misdiagnosed with benign breast diseases. There are relatively few such studies; one of the largest includes 80 patients, of whom 14% subsequently developed invasive breast cancer [5]. A combined analysis of these reports demonstrated an average progression rate of 43% in women with untreated DCIS [6]. One small longitudinal study described a cohort of 28 women diagnosed with low-grade, non-comedo DCIS by needle biopsy in the 1970s, none of whom underwent primary surgical resection [7]. With 30-years follow-up, 11 women (39.3%) eventually developed invasive breast cancer, and five of these died with metastatic disease. Of the 11 cases of invasive breast cancer, the majority occurred within 10 years of the biopsy, but three cases developed between 23 and 42 years after diagnosis. One limitation of these analyses is the clinical applicability, as there is no evidence that DCIS noted on screening studies will behave in a similar manner to these cases discovered by retrospective review. The biology of screen-detected DCIS has been a focus of recent controversy.

Several groups have drawn attention to the potentially benign nature of screen-detected DCIS and the risk of overdiagnosis. In a summary of seven autopsy series, which described women who died of causes other than breast cancer, the median prevalence of DCIS was 8.9% [8]. The Canadian National Breast Screening Study-2 further supported overdiagnosis [9]. In this randomized study, women were screened with mammography and clinical breast examination versus clinical breast examination alone. After 13 years of follow-up, there was no difference in breast cancer mortality rates, despite a four-fold increase in the detection of DCIS in the mammography group.

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The mortality rates associated with DCIS appear to have decreased with the implementation of screening. Based on data from the Surveillance, Epidemiology and End Results (SEER) program comparing women diagnosed with DCIS between 1978 and 1983 to women diagnosed between 1984 and 1989, the 10-year breast cancer mortality rate fell from 3.4\% to 1.9\% [10]. Yet, there are data indicating that screen-detected DCIS may actually be more aggressive than symptom-detected DCIS. Evans et al. [11] noted that screen-detected DCIS was more commonly of high grade and more likely to contain necrosis than symptom-detected DCIS, with only 13\% of screen-detected lesions being classified as low grade. De Roos et al. [12] found 53\% of screen-detected DCIS to be high grade and described a more aggressive tumor profile among these lesions.

There are no randomized data to define the natural history of DCIS, as resection has become standard therapy and is highly effective. In general, the 10-year mortality rate from excised DCIS is low, with population-based estimates less than 2\% [10]. In light of these favorable outcomes with treatment and the observation that screen-detected DCIS is often of high-grade, the validity of existing treatment algorithms is supported, and observation is not a strategy frequently employed.

**DETECTION**

Currently, the majority of detected DCIS occurs as a result of identification by a mammogram [13]. Increasingly, MRI is being utilized in the diagnostic and pre-treatment evaluation of patients with DCIS [14]. However, the precise role of MRI in the management of DCIS is not well established. One of the proposed advantages of MRI is its increased sensitivity. The screening mammography for detection of DCIS has been estimated at 86\%, higher than the sensitivity for invasive breast cancer [15]. The sensitivity of MRI for detecting DCIS is higher, estimated between 77\% and 96\% [16,17]. Higher sensitivity provides the potential theoretical advantages of fewer re-excisions, early detection of contralateral disease, and a greater likelihood of planning proper surgical intervention [18]. In addition, one might think that the high negative predictive value of MRI might serve to reduce the number of patients choosing prophylactic mastectomy [19]. However, preliminary data on invasive and non-invasive breast cancers from several authors and the ‘Comparative effectiveness of MRI Imaging in breast CancEr’ (COMICE) trial, randomizing women from the UK with newly diagnosed breast cancer to MRI versus no MRI prior to operation, indicated just the opposite finding; more women having MRI chose contralateral prophylactic mastectomy and had higher initial mastectomy rates [20–24]. The use of MRI prior to partial mastectomy did not reduce the rates of re-excision or of conversion to mastectomy.

While not yet completely validated, the use of MRI currently does impact treatment decisions. A review of 207 women with early stage breast cancer who were candidates for lumpectomy revealed that MRI effected clinical decisions in 43 (20\%) cases [25]. Considering the outcomes and pathologic results, the authors reported that 11\% had favorable changes in treatment attributed to MRI while 6\% had unfavorable changes. In another study of 54 patients with DCIS, MRI altered surgical management in 26\% of cases. MRI prevented additional surgery in 15\% of patients but led to negative surgical interventions in 11\% of patients [26].

The use of MRI is associated with pitfalls and disadvantages. One of the greatest is its cost, which may preclude routine widespread use. In addition, the lack of availability of MRI-guided biopsy in some facilities may prevent investigation of abnormalities detected by MRI for which there is not an ultrasound or mammogram correlate [13]. While the greater sensitivity of MRI may be an advantage, it also lends itself to overtreatment with the potential for unnecessary biopsies and an overestimation of the extent of disease resulting in wider surgical margins [27]. Comparison to surgical specimens has suggested that MRI overestimates the size of the lesion by over 2-fold in 23\% of patients, particularly with heterogeneous abnormalities [28]. While many stress the importance of detecting occult contralateral cancers, it should be appreciated that the rate of new contralateral breast cancers 5 years after systemic adjuvant treatment is low [29]. MRI likely has a role in the management of DCIS, but at this time it should not replace mammography. In the absence of enrollment in a clinical trial to determine the merits of breast MRI, the use of MRI should be applied to specific clinical circumstances and not routinely employed.

**LOCAL TREATMENT-SURGERY AND RADIATION THERAPY**

Resection remains the primary treatment for DCIS, though the optimal strategy has yet to be defined. Mastectomy is the historical standard and offers a very high chance of cure, with a reported 98–99\% local recurrence-free survival at 10 years [30]. For many patients, however, mastectomy may be overtreatment and margin-negative lumpectomy has emerged as a good option. There are no randomized trials comparing mastectomy with lumpectomy for women with DCIS, but retrospective studies have failed to demonstrate any benefit in breast cancer-specific or overall survival between these two strategies [31,32]. These studies do show a higher risk of recurrence after lumpectomy, though this difference can be diminished by the addition of radiation therapy. It is not clear whether all women with lumpectomy require radiation therapy. Selecting an appropriate treatment strategy can be challenging and must reflect patient and tumor characteristics as well as patient preference. While there is controversy surrounding optimal management of patients with DCIS, several studies have provided useful insight.

In the prospective National Surgical Breast and Bowel Project (NSABP) B-06 trial, women with invasive breast cancer were randomized to mastectomy or lumpectomy with or without whole breast radiation [33]. Included in this trial were 76 women who, upon closer review of their biopsy specimens, were found to have DCIS and had longitudinal follow-up [34]. Of these patients, 48 were treated with lumpectomy and 28 underwent mastectomy. The local recurrence rate was 7\% in 27 patients who had lumpectomy with whole breast radiation and 43\% in 21 patients who had lumpectomy without radiation. Fifty-five percent of recurrences were invasive cancers. In a population-based cohort of 1,036 women with DCIS treated with lumpectomy alone, the 5-year risk of local recurrence was 20.2\%, with 8.2\% presenting with recurrent DCIS and 11.7\% presenting with invasive cancer [35].

These relatively high rates of local recurrence led to the establishment of NSABP B-17, which randomized 918 women with DCIS to either lumpectomy alone or lumpectomy with radiation therapy [36]. There was no difference in survival rates between the two study arms, but the 5-year event-free survival rate was greater in women who received radiation (84.4\% vs. 73.8\%). Of the 137 local recurrences, 39\% harbored some component of invasive breast cancer. A similar prospective trial conducted by the European Organisation for Research and Treatment of Cancer (EORTC) 10853 randomized over 1,000 women with excised DCIS to whole breast radiation or no further treatment [37]. Again, there was no difference in survival rates, but 10-year local recurrence-free survival rate favored women treated with radiation (85\% vs. 74\%), and 52\% of the recurrences included an invasive component.

**Optimal Margins of Excision**

Decisions regarding optimal surgical management must consider surgical margins, as margin width has proven to be an important variable associated with recurrence [38]. Inadequate margins may
lead to increased recurrence rates, but excessively wide margins may lead to poor cosmesis without added benefit. In a retrospective review of mastectomy specimens from women treated for DCIS, margins of 2 mm or less had a local failure rate of 16%, compared to 2% for patients with margins over 2 mm ($P = 0.0356$) [39]. This study failed to demonstrate a benefit to margins of 10 mm or greater in women receiving mastectomy.

Optimal margins for lumpectomy patients are less clear. In the absence of radiation therapy, the lowest local recurrence rates are associated with wide margins of 10 mm or greater with increasing failure rates for margins of 1–9 mm and margins under 1 mm, independent of other prognostic factors. Among patients with margins greater than 10 mm, regardless of radiation use or other prognostic factors, there was a consistently low local recurrence risk of 3% at 8 years [40]. When adjusting for other predictors of recurrence such as age at diagnosis, nuclear grade, and tumor size, patients with margins less than 10 mm were at a 5.39-fold greater risk of local recurrence than patients with margins of 10 mm or more (95% confidence interval, 2.68–10.64) [41]. However, when radiation was added to lumpectomy, there appeared to be no incremental benefit to these wider margins. In a meta-analysis, the effect of margin status was investigated for patients who had lumpectomy with radiation therapy. In this analysis, there was no justification for routine use of margins of 10 mm or greater in patients treated with lumpectomy and radiation [42]. Higher rates of recurrence were observed with margins under 2 mm. However, no further benefit was shown when margins of 2 mm or greater were compared with margins of 5 mm or greater. These data implied that for women receiving lumpectomy and radiation, a margin of 2 mm or greater is adequate to ensure local recurrence rates. But, there are no prospective randomized studies addressing this question. If adequate margins are not likely to be obtained with lumpectomy, mastectomy should be pursued.

If adequate margins can be obtained by either lumpectomy or mastectomy, the decision is often left to patient preference, though there are several important variables to consider. If there are contraindications to radiation, patients should be offered mastectomy. Mastectomy and reconstruction may be a preferred option if lumpectomy is unlikely to achieve an acceptable cosmetic result. Patients with multifocal disease have an increased risk of recurrence after lumpectomy, though this risk is reduced with whole breast radiation [43]. Patients with a genetic predisposition to breast cancer, such as carriers of BRCA1 or BRCA2 mutations or those with a strong family history of breast cancer, may also elect for mastectomy. Patients with BRCA1 or BRCA2 mutations have a high risk of developing ipsilateral and contralateral second primary tumors [44]. The estimated 10-year risk of developing contralateral breast cancer in BRCA mutation carriers ranges from 20 to 40%, compared to the 5–10% risk in the general population. When advising patients of their treatment options, this information may influence the decision in favor of mastectomy, in addition to the diminished need for post-mastectomy surveillance [45].

**Predicting Recurrence Risk After Excision**

In the absence of these specific circumstances, the risk of recurrence after lumpectomy can be further clarified using the University of Southern California/Van Nuys Prognostic Index (USC/VNPI) [46]. These criteria were based on retrospective analysis of 706 women with DCIS treated with either excision alone or excision followed by radiation therapy. The USC/VNPI incorporated four variables and assigned each variable 1–3 points, generating a score from 4 (best prognosis) to 12 (worst prognosis). The variables were tumor size, margin width, pathologic classification (based on grade and presence or absence of comedo-type necrosis), and patient age (Table I). Among patients with scores of 4, 5, or 6, there was no statistical difference in 12-year local recurrence-free survival between patients who received excision alone or excision with radiation. Patients with scores of 7 or higher did demonstrate a statistically significant improvement in local recurrence-free survival with the addition of radiation. For patients with scores of 7, 8, or 9, there was a 12–15% decrease in local recurrence rates with the addition of radiation after lumpectomy. Patients with scores of 10, 11, or 12 had the greatest absolute benefit from radiation but still had very high local recurrence rates, approaching 50% at 5-year follow-up.

Analysis of patients from NSABP B-17 confirmed the prognostic utility of pathologic characteristics [47]. The presence of comedonecrosis was found to be an independent marker of higher risk of recurrence in either treatment group. Analysis of a large population-based cohort treated with lumpectomy alone revealed that high grade was associated with recurrence of either DCIS or invasive cancer [36]. This study also confirmed that narrow margins and lower age were both associated with recurrence.

In sum, these data suggested there exists a subset of patients with low risk DCIS who may be treated with surgery alone. They also suggested that there is a subset of patients for whom the risk of recurrence after lumpectomy and radiation is unacceptably high, and mastectomy is a preferable option. Prospective studies using these criteria to guide management have not yet been performed.

**AXILLARY NODE SAMPLING**

By definition, DCIS does not violate the basement membrane and metastases should not be possible. However, certain types of DCIS are associated with axillary lymph node metastases and poorer prognosis. Historically, axillary lymph node metastases in patients with pure DCIS were uncommon (<1%) [48]. However, recent studies have reported a higher incidence of axillary lymph node metastases with a reported range from 1.4% to 12%, as outlined in Table II [49–55]. While axillary staging plays a role in some women with DCIS, the incidence of axillary node metastases is still relatively uncommon, and axillary dissection is not indicated in patients with DCIS. As a result, sentinel lymph node biopsy (SLNB) has become more commonly used in the management of selected patients with DCIS.

There are several studies describing SLNB in patients with DCIS. One, from Moffitt Cancer Center, was a retrospective analysis of 87 patients with newly diagnosed, pure DCIS who had SLNB [55]. Five (6%) of 87 were SLN-positive. Of these five, four had comedonecrosis, suggesting more aggressive tumor biology. Analysis of 854 patients with DCIS treated over 10 years at the European Institute of Oncology revealed a 1.4% (12/854) incidence of SLN metastases [52]. Characteristics associated with SLN metastases

### Table I. University of Southern California/Van Nuys Prognostic Index for DCIS

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
<th>1 point</th>
<th>2 points</th>
<th>3 points</th>
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<tbody>
<tr>
<td>Size</td>
<td>15 mm or less</td>
<td>16–40 mm</td>
<td>41 mm or more</td>
<td></td>
</tr>
<tr>
<td>Margin score</td>
<td>10 mm or more</td>
<td>1–9 mm</td>
<td>Less than 1 mm</td>
<td></td>
</tr>
<tr>
<td>Pathologic classification score</td>
<td>Non-high grade without comedo-type necrosis</td>
<td>Non-high grade with comedo-type necrosis</td>
<td>High grade</td>
<td></td>
</tr>
<tr>
<td>Age score</td>
<td>61 years or older</td>
<td>40–60 years</td>
<td>30 years or younger</td>
<td></td>
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included age <50 years, tumor size over 30 mm, and presentation with a palpable mass or mass. This study demonstrated a low incidence of SLN metastases in cases of pure DCIS. The authors suggested that preoperative invasive procedures like core biopsy, fine needle aspiration, and excisional biopsy might displace epithelial cells, facilitating passive transport to the axillary lymph nodes. Another explanation is a sampling error in cases of extensive DCIS, whereby a focus of microinvasive cancer is missed, and the tumor is misclassified as pure DCIS prior to excision.

Although high-risk characteristics have been defined for pure DCIS, controversy remains regarding the utility of SLNB in these patients. ASCO guidelines recommend SLNB in patients undergoing mastectomy for DCIS. Because of a significant risk of upstaging from DCIS to invasive cancer when doing a mastectomy, it is appropriate to offer a SLNB to this group of patients. Axillary lymph node dissection may be avoided in patients who are found to be SLN-negative and have invasive breast cancer on final pathology. However, according to current ASCO guidelines, routine SLNB is not recommended in patients with DCIS undergoing segmental mastectomies.

**Sentinel Node Biopsy for DCIS With Microinvasion**

DCIS with microinvasion is a subset of T1 breast cancer designated as T1mic. According to the 2010 American Joint Committee on Cancer Staging Handbook, microinvasive DCIS (DCISM) has invasion of cancer beyond the basement membrane measuring less than 1 mm in its greatest dimension [57]. This subset of DCIS has a different biology than pure DCIS, with a greater potential for metastases. In a cohort of 41 consecutive patients with DCISM, SLNB revealed four SLN-positive patients (9.7%) [56]. These patients then received a full axillary node dissection, and three of the four patients had no additional nodal involvement. Other studies have demonstrated a similar incidence of SLN metastases ranging from 9.7 to 14% in patients with DCISM (Table II) [49,50,56]. Data from the American College of Surgeons Oncology Group Z0011 randomized trial described locoregional recurrence rates after SLNB with or without axillary dissection in patients with T1 or T2 cancers and sentinel lymph node metastases. The results of this trial demonstrated that SLNB without completion axillary dissection offered excellent regional control and was reasonable for node-positive patients with early-stage cancers treated with breast-conserving therapy, whole breast radiation, and adjuvant systemic therapy [58].

**SYSTEMIC THERAPY FOR DCIS**

**Tamoxifen in the Adjuvant Setting**

Given the role of estrogen in the pathogenesis of breast cancer, therapeutic strategies targeting the estrogen pathway have received a great deal of attention. Much of the early research involved tamoxifen, a selective estrogen receptor modulator (SERM). While tamoxifen has the properties of an estrogen agonist at some sites, including bone and the endometrium, it serves as a potent estrogen antagonist in breast tissue. These properties led to the study of tamoxifen as an adjuvant treatment in patients with invasive breast cancer where it was found to reduce the risk of recurrence and death after excision [59]. These results formed the rationale to explore adjuvant tamoxifen in women with resected DCIS, based in part on the assumption that DCIS is either a precursor of invasive breast cancer or is a risk factor for the development of invasive breast cancer.

The role of adjuvant tamoxifen in the treatment of patients with resected DCIS was examined in two large trials, the NSABP B-24 trial and the UK/ANZ trial. These trials were designed at a time when breast-conserving surgery was being developed, and as a result, surgical management in both trials consisted of lumpectomy. In NSABP B-24, patients received radiation after lumpectomy, based on data from the preceding NSABP B-17 trial [60]. The UK/ANZ trial used a two-part randomization scheme to examine the benefits of both tamoxifen and radiation. The results for the two studies demonstrated a benefit to adjuvant tamoxifen after lumpectomy.

NSABP B-24 enrolled 1,804 patients with DCIS having lumpectomy between 1991 and 1994 [61]. Patients with positive microscop ic margins were not excluded, and all were treated with radiation (50 Gy) within 8 weeks of surgery, then randomized to receive either tamoxifen 10 mg daily for 5 years or placebo. Analysis after 7 years of follow-up revealed a 39% reduction in the cumulative incidence of breast events with tamoxifen versus placebo [62]. The overall reduction in ipsilateral invasive and non-invasive breast tumors was 31% with adjuvant tamoxifen. Tamoxifen was associated with a reduction in ipsilateral invasive tumors versus placebo from 5.3 to 2.6% ($P = 0.01$) but not with a reduction in ipsilateral non-invasive tumors. There was also a reduction in contralateral breast tumors by 53% with an absolute reduction from 4.9% in the placebo arm to 2.3% in the tamoxifen arm. This reduction in contralateral tumors was not statistically significant for invasive breast tumors (3.2–1.8%, $P = 0.16$) but was significant for non-invasive breast tumors ($P = 0.03$).

The UK/ANZ trial had similar entry criteria and enrolled 1,701 patients between 1990 and 1998 following lumpectomy for DCIS [63]. In contrast to the NSABP B-24 study, this trial required clear surgical margins and employed a 2 × 2 randomization scheme to examine the benefits of both radiation and tamoxifen. The first randomization was to adjuvant radiation after lumpectomy or lumpectomy alone. The second randomization was to tamoxifen 20 mg daily or placebo for 5 years. Patients could enter either or both randomizations, and 1,576 entered the tamoxifen randomization. After a median follow-up of 12.7 years, tamoxifen was associated with a 29% reduction in the cumulative incidence of breast events [64]. The overall reduction in ipsilateral breast events was 22% with adjuvant tamoxifen, with a 30% reduction in ipsilateral DCIS and a 5% reduction in contralateral breast cancer.

### Table II. Incidence of Positive SLN in Women With DCIS

<table>
<thead>
<tr>
<th>Reference</th>
<th>Positive SLN in pure DCIS (%)</th>
<th>Positive SLN in DCISM (%)</th>
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<tbody>
<tr>
<td>Pendas et al. [55]</td>
<td>5/87 (6%)</td>
<td>3/31 (10.0%)</td>
</tr>
<tr>
<td>Klauber-DeMore et al. [50]</td>
<td>9/76 (12.0%)</td>
<td>4/41 (9.7%)</td>
</tr>
<tr>
<td>Intra et al. [51,56]</td>
<td>7/223 (3.1%)</td>
<td></td>
</tr>
<tr>
<td>Moore et al. [53]</td>
<td>43/470 (9.0%)</td>
<td></td>
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<tr>
<td>Dominguex et al. [54]</td>
<td>16/158 (10.0%)</td>
<td></td>
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<tr>
<td>Intra et al. [52]</td>
<td>12/854 (1.4%)</td>
<td></td>
</tr>
<tr>
<td>Sak et al. [49]</td>
<td>5/49 (10.0%)</td>
<td>2/20 (10.0%)</td>
</tr>
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SLN, Sentinel Lymph Node biopsy; DCIS, Ductal Carcinoma In Situ; DCISM, Ductal Carcinoma In Situ Microinvasive
reduction in ipsilateral invasive cancers. There was also a 56% reduction in contralateral breast tumors. There was no significant difference in mortality rates between any of the treatment arms.

Both of these large studies demonstrated a benefit from adjuvant tamoxifen. The absolute incidence of recurrent breast cancer, both invasive and non-invasive, was higher in the NSABP study, which may have reflected the inclusion of women with positive surgical margins after lumpectomy. In addition, while tamoxifen did demonstrate a benefit in recurrence risk, there was no impact on overall survival in either trial. The benefits of tamoxifen from these two adjuvant trials are reflected in the 2011 National Comprehensive Cancer Network (NCCN) guidelines, which recommend consideration of tamoxifen for 5 years as risk reduction therapy in patients treated with lumpectomy alone or with lumpectomy and radiation [65].

Tamoxifen in the Prevention Setting

In addition to the decreased risk of local recurrence, the early randomized adjuvant trials of tamoxifen in the treatment of invasive breast cancer also revealed a reduction in the incidence of contralateral breast cancers. This suggested a potential role for tamoxifen in the prevention of breast cancer, and several large studies emerged exploring tamoxifen as primary prevention in high-risk women. Two of the initial trials began accrual in 1992. The NSABP launched the Breast Cancer Prevention Trial (P-1) in the USA, and the International Breast Cancer Intervention Study (IBIS-I) began accrual in Europe. Both studies enrolled women at high risk of developing breast cancer, randomizing subjects to receive tamoxifen, 20 mg daily, or placebo for 5 years.

NSABP P-1 defined high risk as either age over 60 years, age of 35–59 years with a 5-year predicted risk for breast cancer of at least 1.66% (based on the Gail model), or a personal history of lobular carcinoma in situ (LCIS) or atypical hyperplasia [66]. Upon completion of the study, 13,388 women had entered randomization. With tamoxifen use, the risk of invasive breast cancer was reduced by 49% (P < 0.00001) and the risk of non-invasive cancer (comprised of both DCIS and LCIS) was reduced by 50% (P < 0.002). These results prompted an unblinding of participants in 2005 and subsequently, almost one-third of the women in the placebo arm began SERM therapy. In an update after 7-years of follow-up, the benefit was less substantial, with a 43% reduction in the risk of invasive breast cancer of a 37% reduction in the risk of non-invasive breast cancer [67]. The attenuation of the benefit of tamoxifen over time may be attributed to the unplanned crossover from placebo to tamoxifen after participants were unblinded.

IBIS-I identified high-risk women using specific entry criteria based on age approximating a two-fold risk for women age 45–70 years, a four-fold risk for ages 40–44 years, and a ten-fold risk for women aged 35–39 years [68]. For women aged 35–39 years, high risk was defined as having a personal history of LCIS, having a first-degree relative with bilateral breast cancer diagnosed before age 40 years, or having at least two first-degree relatives with breast cancer diagnosed before age 50 years. For women aged 40–44 years, high risk was defined as having atypical hyperplasia, having a first-degree relative with bilateral breast cancer diagnosed before age 50 years, or having at least two first-degree or second-degree relatives with breast cancer diagnosed before age 50 years. For women aged 45–70 years, high risk was defined as the presence of any of the following criteria: (1) having a first-degree relative who developed breast cancer at or before age 50 years; (2) having a first degree relative with bilateral breast cancer; (3) having at least two first-degree or second-degree relatives with breast cancer; (4) a personal history of either LCIS or atypical hyperplasia; or (5) nulliparity or a personal history of a benign breast biopsy in a woman with a first-degree relative who developed breast cancer at any age. IBIS-I randomized 7,152 women at high risk to either tamoxifen or placebo. And after 50 months of follow-up, tamoxifen was associated with a 32% risk reduction in breast cancer (95% confidence interval 8–50), applied to both invasive (25%) and non-invasive cancer (69%).

Despite the benefits of tamoxifen shown in these studies, there was concern regarding adverse effects, particularly given the lack of an overall survival benefit and the relatively small absolute benefit to tamoxifen in women treated in the high-risk setting. While tamoxifen is a competitive antagonist of the estrogen receptor in breast tissue, it retains agonist properties in the endometrium, which leads to an increased risk of endometrial cancer with aging [69]. The NSABP P-1 study described a relative risk of 3.28 though all cases were FIGO stage I and there were no deaths attributed to endometrial cancer. The risk appeared to be greatest in women over 50 years of age. The relative risk in women younger than age 50 years was 1.42 (95% confidence interval of 0.55–3.81), whereas the risk in women age 50 years and older was 5.33 (95% confidence interval of 2.47–13.17). The IBIS-I study also revealed an increased risk in endometrial cancer with tamoxifen, though the risk in this study was not statistically significant.

Another important adverse effect associated with tamoxifen was an increased risk of thromboembolic events. The updated NSABP P-1 data identified an increased risk of pulmonary embolism (RR 1.21, 95% confidence interval 1.08–4.51) and non-significant increases in deep venous thrombosis (RR 1.44, 95% confidence interval 0.91–2.30) and stroke in women age 50 years and older (RR 1.13, 95% confidence interval 0.97–2.22). The IBIS-I data also showed an increased risk in thromboembolic events (OR 2.5, P = 0.001) associated with tamoxifen use. Cataracts were more commonly described with tamoxifen use with a relative risk in the updated NSABP P-1 data of 1.21 (95% confidence interval 1.10–1.34). One advantage of tamoxifen was the decreased risk of osteoporotic fracture. The updated NSABP P-1 data revealed a 32% reduction in osteoporotic fracture with tamoxifen compared to placebo (RR 0.68, 95% confidence interval 0.51–0.92). In both of these prevention studies, use of tamoxifen did not impact overall or cause-specific survival.

Tamoxifen and Raloxifene in the Prevention Setting

Given the concern regarding adverse effects, the NSABP launched a second, large prevention trial that compared tamoxifen with raloxifene, a second generation SERM. This study was in part based on findings from a trial that showed raloxifene reduced the risk of ER+ invasive breast cancer by 72% during 4 years of treatment in post-menopausal women with osteoporosis [70]. The NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 Trial enrolled 19,747 post-menopausal women (mean age 58.5 years) with an increased 5-year breast cancer risk (at least 1.66% based on the Gail model) [71]. Participants were randomized to receive either tamoxifen 20 mg daily or raloxifene 60 mg daily continuously for 5 years. An update of these data showed that the relative risk of invasive breast cancer was 1.24, favoring the tamoxifen arm (P = 0.01), suggesting that raloxifene was approximately 76% as effective as tamoxifen in preventing invasive breast cancer [72]. The relative risk of non-invasive breast cancer was 1.22, again favoring the tamoxifen arm though this did not reach statistical significance (P = 0.12). Raloxifene had a more favorable adverse effect profile, with a lower incidence of uterine cancer and thromboembolic complications. The relative risk of uterine cancer was 0.55 favoring raloxifene (P = 0.003) though the absolute numbers were small in both arms (2.25 per 1,000 with tamoxifen vs. 1.23 per 1,000 with raloxifene). Thromboembolic complications were seen at a rate of
3.30 per 1,000 with tamoxifen and 2.47 with raloxifene, which correlated to a relative risk of 0.75 favoring raloxifene ($P = 0.007$).

All of these studies demonstrated benefit to the use of tamoxifen, either as a systemic adjuvant therapy after lumpectomy and radiation for DCIS or as an agent of primary prevention. That benefit was tempered by the adverse effects of tamoxifen, including the risk of endometrial cancer and thrombosis. In the adjuvant setting, certain predictive markers may be helpful in deciding who should receive post-operative tamoxifen. For example, review of the available surgical specimens from the NSABP B-24 trial identified that micropapillary tumor type, comedo necrosis, or tumor size of at least 1 cm were associated with increased risk of ipsilateral recurrence and contralateral breast cancers [73].

**Expression of Hormone Receptors in DCIS**

The expressions of the estrogen receptor (ER) or the progesterone receptor (PR) are accepted prognostic markers in the management of invasive breast cancer. Their use in the management of DCIS is felt to be a reasonable extrapolation; however, prospective data are lacking. Neither NSABP B-24, nor the UK/ANZ adjuvant trials limited inclusion to women whose tumors expressed ER or PR. Retrospective analysis of ER expression in samples from the NSABP B-24 study did suggest a predictive role for ER expression [74]. Of the 1,804 patients enrolled in the study, ER status was determined for 628 (327 in the placebo arm and 301 in the tamoxifen arm), and 482 tumors (77%) were ER-positive. In the subset of ER-positive patients, tamoxifen reduced the risk of ipsilateral recurrence and contralateral breast cancers. The overall relative risk was 0.41 (95% confidence interval 0.25–0.65, $P = 0.0002$). The benefit of tamoxifen in patients with ER-negative tumors was less significant (RR 0.80, $P = 0.51$), although the small sample size and small number of events precluded definitive conclusions. The NCCN established a task force on ER and PR testing in breast cancer, which concluded that ER and PR expression should be measured using standardized immunohistochemistry (IHC) on all samples of DCIS [75]. Treatment recommendations were restricted to patients with ER-positive DCIS, with the benefit of tamoxifen for ER-negative DCIS remaining as unknown. In 2010, the American Society of Clinical Oncology (ASCO) released recommendations detailing the testing of hormone receptors in breast cancer [76]. While the panel felt there was value in assessing ER status in DCIS, the lack of validation studies precluded formal recommendations, and the panel left the decision for ER testing to the patient and treating physician.

**Aromatase Inhibitors as Adjuvant Treatment for DCIS**

Another unanswered question in the management of DCIS is the role of aromatase inhibitors. In post-menopausal women, adjuvant use of aromatase inhibitors has proven more effective than tamoxifen in reducing recurrence and preventing new contralateral breast cancers after local therapy for invasive breast cancer [77]. It stands to reason that aromatase inhibitors could play a role in the adjuvant treatment of DCIS in post-menopausal women. This led to the design of the second International Breast Cancer Intervention Study (IBIS-II), which explores the role of aromatase inhibitors in both primary prevention and as adjuvant therapy after lumpectomy and radiation for DCIS [78]. The prevention arm will randomize 6,000 post-menopausal women with a high risk of breast cancer to either anastrozole 1 mg daily or placebo for 5 years. The adjuvant arm will randomize 4,000 women with completely excised DCIS to either tamoxifen 20 mg daily or anastrozole 1 mg daily for 5 years. The ongoing NSABP B-35 study poses a similar question, comparing adjuvant tamoxifen 20 mg daily with anastrozole 1 mg daily for 5 years in 3,000 post-menopausal women undergoing lumpectomy and radiation for DCIS [79].

**HER-2/neu Overexpression**

HER-2/neu is overexpressed in many cases of DCIS, though the precise incidence is unclear. In a single institution review of 103 patients with DCIS, HER-2/neu was overexpressed in 61% of cases [80]. In contrast, another single institution review of 106 patients with DCIS noted HER-2/neu overexpression in only 37% of cases [81]. This study also described an association between HER-2/neu overexpression and the detection of invasive foci on surgical specimens. The correlation between HER-2/neu and tumor behavior has been previously described. A retrospective analysis was performed on women enrolled on the EORTC trial 10853, which randomized women to wide local excision or excision plus radiation for DCIS. In the subset of women who experienced local relapse, HER-2/neu was overexpressed in 24 of 31 patients (77%) [82]. The true significance of HER-2/neu overexpression in the management of DCIS is under investigation, fueled by its clear role in invasive breast cancer as a prognostic factor and a predictive factor for the use of trastuzumab, a monoclonal antibody targeting HER-2/neu. The use of trastuzumab in the management of DCIS is appealing given the relatively frequent overexpression of its target and the lack of effective medical therapy for DCIS that does not express ER. This has led to the development of two ongoing clinical trials exploring the role of trastuzumab in DCIS. One study is being conducted at M.D. Anderson Cancer Center and investigates the benefit of a single dose of neo-adjuvant trastuzumab in women with DCIS < 1 cm overexpressing HER-2/neu [83]. The primary objectives of this trial are to determine the effect of trastuzumab on the proliferation rate and apoptotic index of HER-2/neu overexpressing DCIS. The other large study is a Phase III trial being conducted by the NSABP enrolling patients that have undergone breast-conserving therapy for DCIS with HER-2/neu overexpression. Patients will be randomized to receive adjuvant radiation alone or with two doses of trastuzumab. In preclinical models, trastuzumab enhanced radiation-induced apoptosis, providing the rationale for this concurrent approach [84,85]. The primary outcome of this trial will be ipsilateral breast cancer events (either invasive or DCIS) and secondary outcomes include incidence of contralateral and distant disease, disease-free, and overall survival.

**Conclusions Regarding Systemic Treatment of DCIS**

The primary role of systemic therapy in the management of DCIS is to prevent recurrent breast events, both invasive and non-invasive. Two large trials have demonstrated a benefit to adjuvant tamoxifen after breast conserving therapy for DCIS. Ongoing studies are examining the use of aromatase inhibitors for post-menopausal women and of trastuzumab for women with tumors with HER-2/neu overexpression, but until these data are reported, the current standard remains tamoxifen. For women treated with mastectomy or in cases where there is no ER or PR expression, the role of adjuvant therapy is undefined. Tamoxifen and, in post-menopausal women, raloxifene are also effective agents for the primary prevention of both invasive and non-invasive breast tumors in women at risk for such events. However, in both the prevention and adjuvant settings, tamoxifen has not shown an impact on overall survival, and its benefit must be weighed carefully against its risks.

**CONCLUSIONS**

DCIS remains a heterogeneous entity with a variable clinical course. The majority of women will be cured with surgery, and incorporation of radiation and tamoxifen to treatment strategies...
have further improved outcomes. Even with these important advances, many challenges remain, including the optimal surgical approach, the proper management of the axilla, identification of patients who may not require radiation, and the development of the ideal systemic therapy. As our understanding of the biology of DCIS grows, so will our ability to tailor therapy to the individual patient.

REFERENCES


