Current Treatment and Clinical Trial Developments for Ductal Carcinoma In Situ of the Breast

JUDY C. BOUGHEY, a RICARDO J. GONZALEZ, b EVERETT BONNER, c HENRY M. KUERER b

aDepartment of Surgery, Mayo Clinic, Rochester, Minnesota, USA; bDepartment of Surgical Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, Texas, USA; cDepartment of Surgery, Memorial Health University Medical Center, Savannah, Georgia, USA

Key Words. Ductal carcinoma in situ • Radiation • Tamoxifen • Trastuzumab

Disclosure: No potential conflicts of interest were reported by the authors, planners, reviewers, or staff managers of this article.

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Discuss the role of radiation therapy in the adjuvant treatment of DCIS.
2. Describe the impact of tamoxifen in the treatment of DCIS.
3. Discuss evolving strategies in neoadjuvant treatment for DCIS.

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ABSTRACT

Ductal carcinoma in situ (DCIS) is the fastest growing subtype of breast cancer, mainly because of the aging of our populations and improvements in diagnostic mammography and core biopsy. DCIS represents a proliferation of malignant-appearing cells that have not invaded beyond the ductal basement membrane and is a precursor for the development of invasive breast cancer (IBC). Approximately 40% of patients with DCIS treated with biopsy alone, without complete excision or further therapy, develop IBC. Most DCIS itself is harmless if it is detected and excised before it can progress to IBC, and the current approach to DCIS treatment is aimed at just that goal. Typically, it consists of multimodal treatment including segmental mastectomy followed by radiation therapy to the whole breast and then hormonal therapy or total mastectomy followed by hormonal therapy.

This review discusses the state-of-the-art in DCIS detection and treatment and highlights promising new strategies in the care of DCIS patients. The data regarding the effectiveness of breast-conserving surgery versus total mastectomy, the possible avoidance of radiation therapy in some subgroups of patients, and the role of hormonal agents are reviewed. Neoadjuvant therapy and the use of trastuzumab for DCIS are currently under investigation and may be future treatment options for DCIS. The Oncologist 2007;12:1276–1287
INTRODUCTION

Ductal carcinoma in situ (DCIS)—also known as noninvasive breast cancer, preinvasive breast cancer, intraductal carcinoma, and breast “precancer”—is a unique classification of clonal proliferation of malignant ductal cells. A broad spectrum of controversial therapeutic options is available to patients with DCIS. In 2005, the incidence of DCIS was approximately 60,000 new cases in the U.S., making it the fastest growing subtype of breast cancer [1]. It is widely accepted that this growing incidence is a result of the increasing use of screening mammography [2]. Risk factors for invasive breast cancer (IBC) and DCIS are similar, including a family history of breast cancer, prior breast biopsies, nulliparity, and late age of first pregnancy [3].

DCIS is considered a noninvasive precursor or marker of IBC. The critical aspects of the diagnosis and treatment of DCIS, respectively, aim to rule out concurrent IBC (present in 10%–25%) and prevent development of invasive carcinoma by means of early diagnosis and management of the DCIS [4–6].

Pathologically, DCIS is described as a proliferation of malignant-appearing cells that have not invaded beyond the basement membrane and is distinguished from IBC by being limited to existing ducts and lobules. It carries malignant potential based on the lesion’s size and histologic grade [7]. The Wellings and Jensen model of the evolution of “ductal carcinoma” shows the natural progression and histological continuum from hyperplasia to IBC, with DCIS immediately preceding invasive cancer (Fig. 1) [8]. This model suggests that an accumulation of molecular changes results in an invasive phenotype. In an analysis of loss of heterozygosity (LOH) in breast cancers, half the proliferative lesions (e.g., low-malignant-potential lesions, such as typical hyperplasia or proliferative disease without atypia, and lesions with significant malignant potential, such as atypical ductal hyperplasia) and 80% of the DCIS shared their LOH patterns with more advanced lesions from the same breast [9]. These findings strongly support a precursor-product relationship between these lesions and the cancers they accompany.

DCIS is classically divided into two major subtypes: comedo carcinoma and noncomedo carcinoma. Histologic subtype is a predictive factor for local failure after breast-conserving therapy (BCT), with comedo-type DCIS having a higher local recurrence rate [10–12]. DCIS is also classified by nuclear grade, a distinct histological feature thought to be related to the behavior of DCIS [13]. High-grade DCIS is more likely to be associated with IBC [14]. High-grade DCIS is commonly associated with necrosis and this combination has the most aggressive biological characteristics. Comedo-type DCIS, high-grade DCIS, and DCIS with necrosis carry a higher local recurrence rate [10]. However, regardless of nuclear grade, the prognosis of DCIS is excellent with low mortality rates.

The natural history of low-grade DCIS can extend more than four decades. IBC develops at or near the same site in the ipsilateral breast as the index DCIS lesion in the majority of women in whom DCIS goes untreated [15, 16]. Sanders et al. [17] reported on the long-term follow-up of 28 women with low-grade DCIS treated by excisional biopsy alone. Eleven women (39%) developed IBC, all in the same breast and quadrant from their initial biopsy. Seven IBCs were diagnosed within 10 years of the DCIS biopsy. Five women developed distant metastasis, which resulted in death 1–7 years after the diagnosis of IBC. These rates of IBC after untreated DCIS are generally in agreement with those reported in other studies (Table 1), in which 47%–86% of women did not develop IBC, even at 20 or more years of follow-up.

This review discusses the state-of-the-art in DCIS detection and treatment and highlights promising new strategies in the treatment and care of patients with DCIS.

DIAGNOSIS OF DCIS

Before the 1970s, prior to use of screening mammography, the diagnosis of DCIS was rare. A 1978 American College of Surgeons survey reported that DCIS constituted <1% of newly diagnosed breast cancers [18]. By 2005, however, mammography use was so common that DCIS was predicted to constitute >20% of breast cancers diagnosed in the U.S. [1]. The majority (90%–95%) of cases of DCIS present as suspiciously grouped, pleomorphic, or fine linear microcalcifications on mammograms, whereas 5%–10% present with a palpable mass or nipple discharge [19, 20].

Breast cancer that is diagnosed by detecting incidental calcifications on mammography is pure DCIS in 65% of cases, DCIS with a focus of invasion in 32%, and IBC in 4% [21]. Stomper et al. [21] examined the relationships between the size and configuration of calcifications and the
presence of IBC. Invasive foci were more likely to be associated with mammographic calcifications ≥11 mm (40%; 77/194) than with calcifications 1–10 mm (26%; 29/110; \(p = 0.019\)). Invasive foci were also more likely to be associated with linear calcifications (44%; 55/126) than granular calcifications (29%; 51/178; \(p = 0.007\)) [21].

The clinical role and impact of breast magnetic resonance imaging (MRI) in the diagnosis of DCIS are evolving. Currently, mammography is the standard of care for the detection and diagnosis of noninvasive breast cancer. Because MRI often misses small, mammographically visible foci, it is not an adequate replacement for mammography in DCIS [22]. The reported sensitivity of MRI is 91%–100% for IBC but only 88%–92% for DCIS [23, 24]. In some cases, MRI does have the advantage: MRI is much more sensitive than mammography in detecting residual disease (97% versus 87%), occult IBC (86% versus 14%), and multicentric lesions (94% versus 38%) [23]. Therefore, MRI has carved a particular niche in the diagnosis of breast cancer. The specificity of MRI, however, has been less promising, with specificity in the range of only 37%–97% [22]. Thus, for now, MRI is still very much a research tool for DCIS.

DCIS is predominantly diagnosed in asymptomatic women identified through mammographic screening. However, autopsy studies identify that 10%–15% of women who never had a clinical diagnosis of breast cancer or DCIS will have evidence of DCIS in their breast [25, 26]. Therefore, diagnosis of DCIS has the potential to overdiagnose women with disease that would never become clinically significant. This is an important point to keep in mind as clinicians weigh the benefits and risks of screening healthy women and the risks/benefits of treatment.

**TREATMENT OUTCOMES IN DCIS**

Historically, the gold-standard surgical approach to DCIS management has consisted of mastectomy and has resulted in nearly 100% disease control [27]. However, BCT (with lumpectomy and adjuvant radiation therapy) has been found to yield excellent local control in IBC, leading to the question of why a more radical surgical procedure should be required for this noninvasive form of breast carcinoma. Experience has assisted in delineating prognostic criteria that can help determine the risk for tumor recurrence and therefore contribute to decisions about when BCT is appropriate for DCIS.

Patients who have large, high-grade DCIS are at the highest risk for developing recurrent DCIS or IBC [11, 28–32]. Two prospective, randomized trials of lumpectomy with or without radiation allowed assessment of prognostic factors. National Surgical Adjuvant Breast and Bowel Project (NSABP) study B-17 evaluated nine pathologic features and found four to be independently related to a higher risk for local recurrence on univariate analysis: the presence of comedo necrosis, solid (rather than cribriform) histologic type, presence of lymphoid infiltrate, and focality [11]. On multivariate analysis, however, only comedo necrosis remained a statistically significant predictor of recurrence. This trial was not designed to prospectively analyze these variables to predict the risk for local recurrence, and therefore these conclusions may relate to an underpowered study. A similar analysis in the European Organization for Research and Treatment of Cancer (EORTC) study 10853 reviewed 863 patients over a median follow-up of 5.3 years. The investigators found that young age (≤40 years) (hazard ratio [HR], 2.14; 95% confidence interval [CI], 1.17–3.91; \(p = 0.02\)), presence of symptoms that led to the detection of DCIS (HR, 1.80; 95% CI, 1.16–2.78; \(p = 0.008\)), growth pattern (cribriform and solid) (HRs, 2.67 and 2.69; 95% CIs, 1.28–5.59 and 1.12–6.47, respectively; \(p = 0.012\)), presence of disease at the surgical margins (HR, 1.74; 95% CI, 1.13–2.68; \(p = 0.009\)) were the most important factors associated with a higher risk for local recurrence [33].

### Table 1. Natural history of untreated DCIS

<table>
<thead>
<tr>
<th>Reference</th>
<th>n of patients</th>
<th>Patients developing IBC (%)</th>
<th>Follow-up (years)</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Page et al. (1982) [69]</td>
<td>28</td>
<td>32</td>
<td>3–31</td>
<td>9.1</td>
</tr>
<tr>
<td>Eusebi et al. (1994) [70]</td>
<td>80</td>
<td>14</td>
<td>1–14</td>
<td>NC</td>
</tr>
<tr>
<td>Collins et al. (2005) [16]</td>
<td>13</td>
<td>46</td>
<td>4–18</td>
<td>13.5</td>
</tr>
</tbody>
</table>

Abbreviations: DCIS, ductal carcinoma in situ; IBC, invasive breast cancer; NC, not calculated.
cinoma [34]. Thus, the standard therapy for DCIS is segmental mastectomy followed by radiation therapy or mastectomy alone. Adjuvant hormonal therapy may be used in hormone-responsive DCIS [35, 36]. As noted, however, the risk for local recurrence depends on several factors and the use of BCT is becoming more common. In this section, we look at surgery, radiation therapy, and systemic therapy for DCIS. In addition, we discuss recent and ongoing or planned investigations into combinations of these modalities and the most likely future direction of the clinical management of this disease.

Surgery for DCIS

Early retrospective studies by Silverstein et al. [28] compared local recurrence among 227 patients with DCIS. Selection criteria for BCT included lesions <4 cm, surgical margins negative for disease, and no evidence of microinvasion on biopsy. Patients not meeting these criteria underwent mastectomy. The 7-year actuarial disease-free survival rate was 98% in patients undergoing mastectomy versus 84% in those receiving lumpectomy with radiation (BCT) \( p = .038 \). There was, however, no significant difference in overall survival in any subgroup comparison, regardless of treatment.

Certainly deciding between BCT and mastectomy involves extensive discussion among the patient, surgeon, radiologist, medical oncologist, and radiation oncologist. A multidisciplinary approach allows for the personalization of care. The major determinant of whether a patient is an acceptable candidate for BCT is the likelihood of obtaining a negative surgical margin. The size of the negative margin is still controversial because there are no definitive data defining an adequate margin. However, there is general consensus that a 2- to 3-mm margin is adequate if adjuvant radiation will be administered. Large tumor size alone is not an absolute indication for mastectomy, but mastectomy should be considered in the setting of large tumors, multicentric lesions, and patients with persistent positive margins after repeated attempts at breast conservation. Furthermore, contraindications to breast irradiation, such as collagen vascular disease and previous irradiation, may require mastectomy rather than BCT in some cases of DCIS. In the U.S., approximately one third of patients with DCIS undergo mastectomy; in centers with unique referral patterns, this rate may be as high as 50% [37].

Traditionally, axillary dissection and sentinel lymph node biopsy have had no role in the management of DCIS. The risk for nodal metastases in patients with DCIS is <3%. The low rate of nodal metastases, the high survival rate of DCIS, and the significant morbidity of an axillary lymph node dissection are reasons why its routine application in the management of pure DCIS is no longer recommended [38]. However, the evaluation of axillary nodes by sentinel lymph node biopsy may be considered, in certain situations, such as larger lesions (>4 cm), palpable lesions, high-grade disease, core needle biopsy–proven microinvasive disease, or when suspicious nodes are evident on axillary sonograms [39]. These particular features increase the risk for nodal metastasis. Klauber-DeMore et al. [40] performed sentinel lymph node biopsy in 76 patients with high-risk DCIS and 31 patients with DCIS with microinvasion. They found that sentinel lymph nodes were positive for disease in 10% of patients with microinvasive DCIS \( n = 31 \) and in 12% of patients with palpable masses, masses evident on mammograms, or extensive high-grade lesions \( n = 76 \). In a European Institute of Oncology study of 223 unselected consecutive patients with pure DCIS, sentinel lymph node biopsy found nodal metastasis, mostly micrometastasis, in 3.1% of patients \( n = 7 \) [41]. More recently, Yen and colleagues evaluated 398 patients with an initial diagnosis of DCIS [42]. Eighty (20%) were found to have IBC in the final pathology analysis. Risk factors for invasive disease were younger patient age (<55 years), large lesions on mammography (>4 cm), high-grade lesions, and a diagnosis made on the basis of core needle biopsy. Fourteen (10%) of the 141 patients who underwent sentinel lymph node biopsy had a positive sentinel node. Multivariate analysis demonstrated that the presence of a palpable lesion was the only predictive factor for sentinel node positivity (odds ratio, 4.28; \( p = .042 \)). These data support the selective use of sentinel lymph node biopsy in DCIS.

Radiation Therapy for DCIS

As the use of BCT for DCIS grows, radiation therapy becomes more important. The role of radiation therapy has been particularly well defined over the last 20 years or so. An early study evaluating the role of radiation in DCIS was NSABP study B-17, which enrolled 818 patients with DCIS that had been excised to clear margins. The patients were randomized to undergo either lumpectomy alone or lumpectomy followed by breast irradiation to a total dose of 50 Gy. At a median follow-up of 43 months, the 5-year event-free survival rate was higher among women who underwent breast irradiation (84.4%) than among women treated by lumpectomy alone (73.8%; \( p = .001 \) [43]. The improvement was a result of a reduction in the occurrence of second cancers in the ipsilateral breast. Radiation therapy resulted in a lower 5-year cumulative incidence rate of second cancers in the ipsilateral breast, 7.5% versus 10.4% for noninvasive cancers and 2.9% versus 10.5% for inva-
sive cancers \( (p = .055 \text{ and } p < .001, \text{ respectively}) \) [43]. Through 12 years of follow-up, updates confirmed that radiation after lumpectomy resulted in a 58% lower incidence rate of all ipsilateral breast tumor recurrences (IBTRs). Local recurrence rates were 17% in patients who did not receive radiation and 8% in patients who did [44]. No difference in survival was seen in this study. All subsets benefited from radiation therapy, regardless of the clinical or mammographic tumor characteristics. Without prospectively evaluating specific risk factors for recurrence, NSABP B-17 demonstrated that breast irradiation after lumpectomy is more effective than lumpectomy alone for women with localized DCIS [43–45].

Other trials have had similar findings. EORTC study 10853 was a randomized phase III clinical trial conducted between 1986 and 1996. More than 1,000 women with clinically or mammographically detected DCIS measuring \( \leq 5 \) cm in diameter who were undergoing BCT were randomized to wide excision alone \( (n = 500) \) or excision and radiation \( (50 \text{ Gy in 5 weeks to the whole breast}, n = 502) \). The 4-year local relapse-free rate was 84% for patients who did not receive radiation compared with 91% for patients who did \( (p = .005) \). Compared with local excision alone, radiation therapy after local excision of DCIS resulted in a lower overall number of recurrences for both invasive and noninvasive disease in the ipsilateral breast at a median follow-up of 4.25 years [46].

A third study was performed in the United Kingdom and Australia and New Zealand (UK/ANZ) over a similar time period (1990–1998). This randomized, controlled trial had a \( 2 \times 2 \) factorial design. In it, 1,701 patients with DCIS detected on screening mammography were randomized to receive radiation or tamoxifen alone, a combination of radiation and tamoxifen, or no adjuvant treatment after complete surgical excision of the DCIS. Radiation resulted in a lower rate of recurrence of DCIS and IBC in the ipsilateral breast and had no effect on cancer in the contralateral breast. Radiation therapy was associated with an 8.9% lower absolute risk for all events in the ipsilateral breast \( (4.8\% \text{ in the irradiated group versus } 13.7\% \text{ in the control group}) \) [36].

These three prospective trials all show that adding radiation to lumpectomy and medical treatment of DCIS statistically decreases patients’ risk for developing recurrent breast cancer (Table 2). This result was recently confirmed in a retrospective review of 307 patients with DCIS who underwent BCT between 1968 and 1998; the median follow-up time was 15 years. Patients who received radiation \( (n = 211) \) had a lower 10-year local recurrence rate \( (8.4\%) \) than those treated with surgery alone \( (n = 92) (29.5\%; p = .003) \) (Fig. 2). The median time to local failure was shorter for patients who did not receive postoperative radiation therapy \( (4.87 \text{ years}) \) than for those who did \( (10.02 \text{ years}; p = .001) \) [47].

### Table 2. Summary of clinical trials evaluating radiation therapy in patients undergoing BCT for DCIS

<table>
<thead>
<tr>
<th>Trial</th>
<th>Follow-up (years)</th>
<th>Breast recurrence rate</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B-17 [44]</td>
<td>12</td>
<td>17%</td>
<td>8%</td>
</tr>
<tr>
<td>EORTC 10353 [46]</td>
<td>4</td>
<td>16%</td>
<td>9%</td>
</tr>
<tr>
<td>UK/ANZ [36]</td>
<td>5</td>
<td>14%</td>
<td>6%</td>
</tr>
</tbody>
</table>

Abbreviations: BCT, breast-conserving therapy; DCIS, ductal carcinoma in situ; EORTC, European Organization for Research and Treatment of Cancer; NSABP, National Surgical Adjuvant Breast and Bowel Project; UK/ANZ, United Kingdom and Australia and New Zealand.
Determining the Need for Radiation Therapy

To determine whether all patients with DCIS require radiation, Silverstein et al. [29] evaluated the effect of margin width on local recurrence. They found that, among patients whose DCIS was excised with margin widths \( \geq 1 \) mm, there was no difference in local recurrence rates between those who did and those who did not receive postoperative radiotherapy [29]. Patients with narrower surgical margins (\(<1 \) mm) had a higher likelihood of recurrence if they did not receive postoperative radiotherapy (relative risk, 2.54; \( p = .01 \)). A recent update of that study reported that the 212 patients who had excision with \( \geq 10 \) mm margins developed 12 recurrences (6%) with a median follow-up of 53 months, compared with the 60 patients who underwent excision plus radiation in whom one recurrence was seen (2%; \( p = .06 \)) [48].

In order to try to validate the findings of Silverstein et al. [29], Harvard researchers conducted a single-arm prospective study of the use of wide excision alone for patients with favorable DCIS, defined as nuclear grade G1 or G2, diameter \( \leq 2.5 \) cm, and excision margins \( \geq 1 \) cm [34]. These patients were treated with surgery alone and no radiation. The trial was stopped early when the number of local recurrences met the predetermined stopping rules. Only 158 patients had been enrolled (the initial target had been 200 patients), and a 2.4% annual rate of disease recurrence in the ipsilateral breast, corresponding to a 5-year recurrence rate of 12%, was reported. Thirty-one percent of these recurrences were invasive. Despite the use of margins \( \geq 1 \) cm, the local recurrence rate was substantial in patients with small, low-grade DCIS lesions treated with excision alone [49].

To date, no subset of patients from randomized clinical trials has been identified that does not benefit from radiation therapy when undergoing BCT for DCIS. The Radiation Therapy Oncology Group (RTOG) accrued patients from 1999 to 2006 for a study comparing whole-breast radiation with or without tamoxifen with no radiation with or without tamoxifen in patients with unifocal, mammographically detected low- or intermediate-grade DCIS \( \leq 2.5 \) cm in diameter and surgical margins \( \geq 3 \) mm. The trial closed early as a result of poor accrual; however, the patients continue to be followed and results are awaited.

The Eastern Cooperative Oncology Group and North Central Cancer Treatment Group designed a prospective trial following 711 low-risk DCIS patients (defined as low- or intermediate-grade DCIS \(<2.5 \) cm or high-grade DCIS \(<1 \) cm) treated with excision (margins \( >3 \) mm) without radiation. The 5-year results of this intergroup study revealed that, in the 580 patients with low- or intermediate-grade DCIS, the ipsilateral breast cancer event rate was 6.8% and the contralateral breast cancer event rate was 3.5% at 5 years. For the 102 patients with high-grade DCIS, the ipsilateral event rate was 14.8% and the contralateral event rate was 4.2% [50]. The authors concluded from this study that selected patients with low- or intermediate-grade DCIS observed without radiation had an acceptable risk for ipsilateral breast cancer events. Further follow-up is needed to document long-term results.

Partial-Breast Irradiation Versus Whole-Breast Irradiation

A significant proportion of patients with DCIS or IBC have difficulty obtaining radiation therapy because of transportation, time, or cost limitations; many of these patients either choose mastectomy over BCT or undergo surgical resection but do not complete radiation therapy [51]. The majority of IBTRs occur in the area of the initial disease and lumpectomy. For these reasons, partial-breast irradiation of the lumpectomy area and surrounding tissue, which can be performed with approaches ranging in duration from 1–3 weeks, are being investigated for both DCIS and IBC.

Accelerated partial-breast irradiation involves radiation of only the excision site and surrounding tissue. Options include brachytherapy (using either a traditional interstitial catheter or the new balloon intracavitary device MammoSite®; Cytyc Corporation, Marlborough, MA) and three-dimensional (3D) conformal external-beam irradiation.

The MammoSite® device is a balloon that is placed within the lumpectomy cavity; radiation (3.4 Gy) is delivered by a seed placed into the center of the balloon twice a day for 5 days. The dose is prescribed to 1 cm from the applicator surface. In 2002, the American Society of Breast Surgeons opened a registry of patients treated with the MammoSite® device. A recent review of the 158 patients with DCIS in this registry, with a mean 7-month follow-up, found that MammoSite® catheter brachytherapy was well tolerated [52]. A multicenter, phase II prospective study of MammoSite® therapy for DCIS has just completed accrual and we await the results and long-term follow-up of this study.

A larger study, designated NSABP B-39/RTOG 0413, is a prospective, randomized, multicenter clinical trial comparing whole-breast irradiation with partial-breast irradiation (Fig. 3). Patients with DCIS or stage I or II IBC, with tumor size \( \leq 3 \) cm and three or fewer positive lymph nodes, are being treated with lumpectomy and then randomized to either whole-breast irradiation to 60 Gy over 6 weeks or partial-breast irradiation (34 Gy by multicatheter brachytherapy, 34 Gy by MammoSite® balloon catheter, or 38.5 Gy by 3D conformal external-beam irradiation). Partial-breast irradiation is given to the index quadrant only, twice
a day, over a 5- to 10-day period. Systemic therapy, if indicated, is given after partial-breast irradiation but before whole-breast irradiation in this protocol. This trial opened in March 2005 with a target accrual of 3,000 patients, which was increased to 4,300 patients in December 2006.

Systemic Therapy for DCIS

Tamoxifen and Other Hormonal Therapies for DCIS
Hormonal therapy with tamoxifen (and sometimes other agents) has become a common component of therapies for hormone-receptor positive DCIS and IBC. NSABP study B-24 was seminal in defining the role of tamoxifen in DCIS. In that trial, conducted in 1991–1995, 1,804 patients with DCIS were treated with excision and radiation (50 Gy) and then randomized to receive either 10 mg tamoxifen \( (n = 902) \) or placebo \( (n = 902) \) twice daily for 5 years, beginning no later than 56 days after surgery. Tamoxifen and radiation were administered concurrently. In that trial, surgical margins were allowed to have tumor involvement. At 5 years, women receiving tamoxifen had fewer breast cancer events, defined as ipsilateral or contralateral invasive or noninvasive disease, than women receiving placebo (8.2% and 13.4%, respectively; \( p = .0009 \)). There were 43% fewer IBC events and 31% fewer noninvasive breast-cancer events in the tamoxifen group [53]. Tamoxifen resulted in absolute 5-year rates of ipsilateral and contralateral breast cancer events that were 3.3% and 1.4% lower, respectively.

The UK/ANZ trial evaluating the role of tamoxifen and radiation in DCIS did not identify a benefit to tamoxifen [36]. Tamoxifen did not significantly reduce the overall event rate, or the rate of invasive breast cancer events. However, it did reduce the overall rate of DCIS (HR, 0.58; 95% CI, 0.49–0.96; \( p = .03 \)). This may be a result of differences in the patient populations. The NSABP B-24 study had a higher proportion of patients younger than 50 (34% versus 10%) and tamoxifen was associated with a greater reduction in hazard for women <50 years old than it was in those >50 years of age.

Despite the documented benefits of tamoxifen in DCIS, adoption of its use has been inconsistent because of patient,
oncologist, and tumor factors. In a retrospective review, researchers evaluated the effect of NSABP B-24’s results on tamoxifen use after surgery for DCIS. The review covered 277 consecutive patients with DCIS treated from 1999 to 2002 at the M.D. Anderson Cancer Center; 166 patients (60%) were offered tamoxifen, and of these, 90 patients (54%) chose to take tamoxifen. Twenty patients (21% of those who initially elected to take tamoxifen) discontinued tamoxifen use because of side effects or complications. Thirty-nine of the 111 patients not offered tamoxifen had documented explanations, including bilateral mastectomy (n = 25), medical reasons (n = 10), and prior use of tamoxifen for other reasons (n = 4). Patients who underwent segmental resection rather than total mastectomy (p = .002) and patients with smaller pathologic DCIS tumors (p = .001) were more likely to be offered tamoxifen than other patients. These two factors were interrelated. Most patients offered tamoxifen (76%) were postmenopausal, compared with the 66% of patients in the group not offered tamoxifen (p = .051) [54]. The omission of tamoxifen may also relate to its toxicity. The absolute reduction in the risk for invasive cancer is ~2% and this may not be worth the potential increase in the risk for thromboembolic events and/or endometrial cancer to some patients or physicians.

A larger study examined treatment trends at eight National Comprehensive Cancer Network designated cancer centers between 1997 and 2004. Overall, 41% of patients with DCIS received tamoxifen, increasing from 24% prior to July 1999, when the results of the NSABP B-24 trial were published, to 46% after. Factors associated with receiving tamoxifen included diagnosis after July 1999, hysterectomy, no history of cerebrovascular or peripheral vascular disease, radiation, and BCT in patients <70 years of age. Tamoxifen use varied significantly among centers, suggesting that physicians vary in how important they view tamoxifen in the reduction of breast cancer risk [55].

Estrogen receptor (ER) status was not a prerequisite for enrollment in the B-24 trial. However, a retrospective analysis of data from NSABP B-24 evaluated the role of ER status in therapeutic response. ER status was known for 676 patients (344 in the placebo group and 332 in the tamoxifen group). At a median follow-up of 8.7 years, 23% of the women who had ER-negative tumors treated with tamoxifen had experienced subsequent breast cancer, compared with 26% of such women in the placebo group. Among patients with ER-positive DCIS, only 10% of women treated with tamoxifen developed breast cancer, compared with 23% who received placebo—a 50% lower rate. Thus, compared with placebo, tamoxifen treatment is associated with an approximately 50% lower risk for subsequent breast can-

<table>
<thead>
<tr>
<th>STRATIFICATION</th>
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<tbody>
<tr>
<td>Age (under 60 versus 60+)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>RANDOMIZATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
</tr>
<tr>
<td>Tamoxifen 20 mg/day and placebo (anastrozole look-alike) For 5 years + Breast Radiation Therapy</td>
</tr>
<tr>
<td>Group 2</td>
</tr>
<tr>
<td>Anastrozole 1 mg/day and placebo (tamoxifen look-alike) For 5 years + Breast Radiation Therapy</td>
</tr>
</tbody>
</table>

**Figure 4.** NSABP B-35 schema.

Abbreviations: DCIS, ductal carcinoma in situ; ER, estrogen receptor; NSABP, National Surgical Adjuvant Breast and Bowel Project; PgR, progesterone receptor.

cer in patients with ER-positive DCIS but has little benefit in patients with ER-negative disease [35].

Tamoxifen is not the only hormonal therapy available, and it is unclear which hormonal therapy is optimal for hormone receptor–positive DCIS. To help answer this question, NSABP conducted B-35, a phase III trial to compare the effectiveness of anastrozole (an aromatase inhibitor) with that of tamoxifen in preventing subsequent breast cancer (local, regional, and distant recurrences and contralateral breast cancer) in postmenopausal women with primary DCIS treated with lumpectomy and breast irradiation (Fig. 4). Patients who had undergone surgery were stratified by age and randomized to tamoxifen (20 mg daily) and breast irradiation or anastrozole (1 mg daily) and breast irradiation. The trial closed to accrual in June 2006 with 3,104 patients enrolled, and results are awaited. In addition to comparing the effectiveness of these two agents in preventing second cancers, the trial will evaluate and compare times to IBC, ipsilateral recurrence, contralateral breast cancer, and other nonbreast second primary cancers; osteoporotic fractures; disease-free survival; and overall survival. B-35 will also ascertain the effects of anastrozole on patients’ symptoms and quality of life and compare them with those seen with tamoxifen.

**Neoadjuvant Systemic Therapy for DCIS**

Multiple studies have demonstrated breast-conservation rates as high as 30% when using neoadjuvant systemic ther-
apy for large invasive tumors [56–58]. A similar approach could be considered for treatment of DCIS, presumably reducing the number of mastectomies for this disease. Neoadjuvant chemotherapy for IBC can result in response of the invasive component, with minimal change in the intraductal component, resulting in residual DCIS. This may be a limiting factor for neoadjuvant chemotherapy for DCIS; however, several lines of evidence suggest that it is logical to use neoadjuvant chemotherapeutic agents or other anticancer drugs in the treatment of DCIS. Systemic hormonal treatment with tamoxifen markedly decreases the risk for breast cancer development in women with high-risk proliferative lesions, such as atypical ductal hyperplasia [53]. Eriksen et al. [59] and Hwang et al. [60] have begun a novel neoadjuvant chemotherapeutic strategy for downstaging DCIS with tamoxifen for patients with DCIS. Their early findings include promising responses detected by MRI in patients with ER-positive DCIS and little response in ER-negative disease.

Recently, it was proposed that trastuzumab (Herceptin®; F. Hoffmann-La Roche, Basel, Switzerland), a monoclonal antibody against human epidermal growth factor receptor (HER)-2/neu, could be effective in the treatment of DCIS—both in downstaging disease to permit less extensive surgery and in preventing the transition of DCIS to IBC. Trastuzumab has yielded promising results in the treatment of HER-2/neu—positive IBC and may also be effective against HER-2/neu—positive DCIS [53]. Trials of standard chemotherapy plus trastuzumab for patients with metastatic and operable breast cancers have reported promising results [61, 62]. Gennari et al. [63] recently treated 11 patients who had early-stage IBC with neoadjuvant trastuzumab, administered in a loading dose of 4 mg/kg and then three weekly doses of 2 mg/kg. The tumor was removed 1 week after the completion of trastuzumab treatment. Five patients had evidence of pathologic response (one complete pathological response, four partial responses). Slamon et al. [62], in a phase III trial, compared trastuzumab in combination with standard chemotherapy (paclitaxel or the combination of doxorubicin and cisplatin) with standard chemotherapy alone as front-line therapy for metastatic IBC expressing HER-2/neu. Results showed that combination therapy was associated with a longer time to tumor progression, greater partial response rate, and longer median survival time. In a similar study by Buzdar et al. [61], patients with HER-2/neu—positive operable IBC were treated in the neoadjuvant setting with paclitaxel and 5-fluorouracil, epirubicin, and cyclophosphamide with or without trastuzumab. Pathologic complete response rates were so dramatically higher with trastuzumab (25% for chemotherapy alone versus 67% for chemotherapy plus trastuzumab) that the data monitoring committee halted the trial early.

Further rationale for studying trastuzumab for the neoadjuvant treatment of DCIS relates to the low number of effective medical treatments for ER-negative DCIS. Almost half of all ER-negative DCIS lesions express HER-2/neu, and a majority of HER-2/neu—positive DCIS lesions are ER negative [42]. Approximately 60% of cases of DCIS overexpress HER-2/neu, and HER-2/neu overexpression is more common in higher-grade and comedo DCIS, both of which are associated with higher local recurrence rates than low-grade and noncomedo DCIS [42, 64–67].

**Current Trials of Trastuzumab for DCIS**

The NSABP is developing a phase III randomized trial of trastuzumab for patients with HER-2/neu—overexpressing DCIS treated with breast-conserving surgery yielding negative margins. Patients will be randomized to receive 6 weeks of whole-breast irradiation with or without concurrent trastuzumab. Two doses of trastuzumab will be given: a loading dose of 8 mg/kg during week 1 of irradiation and a final dose of 6 mg/kg during week 3. The primary endpoint for the trial is any cancer event, and the secondary endpoints include IBTR or development of contralateral breast cancer. Approximately 1,000 patients will be needed for this trial.

The M.D. Anderson Cancer Center has recently begun a trial of neoadjuvant trastuzumab for DCIS. We hypothesize that trastuzumab will have substantial activity against DCIS, perhaps even more than it has against IBC, because the volume of disease in DCIS patients is normally much lower than in IBC patients. The design of this trial of neoadjuvant trastuzumab for DCIS is outlined in Figure 5. To be eligible for the trial, patients must have mammographically detected, nonpalpable, core biopsy—proven DCIS lesions <1 cm in diameter and must have HER-2/neu overexpression or amplification of the her-2/neu gene. Patients with DCIS diagnosed by excisional biopsy are excluded. ER and Her-2/neu expression are determined by immunohistochemical analysis and fluorescence in situ hybridization using tissue obtained during the initial biopsy. Other variables examined in the biopsy tissue are expression of other key molecular markers, tumor proliferation rate, expression of monoclonal antibody to Ki-67, and apoptotic index. The same variables are examined postoperatively in lumpectomy or mastectomy specimens. We hope that this early feasibility study will help pave the way for further studies with larger groups of patients designed to establish the therapeutic efficacy of neoadjuvant trastuzumab for DCIS.

**Patient Perception of DCIS**

Patient perceptions of DCIS vary and although DCIS is distinct from IBC and is not typically life-threatening, patients with DCIS tend to view the disease very much like IBC. A
self-administered survey conducted by Rakovitch et al. [68] compared the perception of risk in patients with DCIS and patients with IBC. That study showed no significant difference between the two groups when comparing the perceptions of risk related to the likelihood of developing local recurrence or dying of breast cancer. Furthermore, the two groups expressed similar levels of psychological distress. Thus, despite their excellent prognosis, women with DCIS express serious concerns and report psychological morbidity similar to that reported by women with invasive cancer. This underscores the importance of patient education to establish accurate perceptions and goals of therapy.

CONCLUSION
DCIS represents a proliferation of malignant-appearing cells in the breast that have not invaded beyond the ductal basement membrane. It is a very late stage of premalignant evolution and is a precursor for the development of IBC; however, it is usually curable if detected and excised before it can progress. Regardless of treatment, the long-term prognosis of DCIS is excellent, with survival rates at 10 years exceeding 95%. Therefore, the challenge in the treatment of DCIS is to balance the risk for local recurrence (especially invasive recurrence) without creating excessive unnecessary morbidity. Today, DCIS is usually diagnosed by mammography and core biopsy. Therapy involves complete surgical excision by either BCT or mastectomy, depending on the area of disease and size of the breast. BCT is usually a reasonable option, as long as all microcalcifications are removed and clear margins of at least 2–3 mm are obtained. Radiation therapy is generally recommended for BCT in DCIS, and in fact, no subgroup of patients has been shown not to benefit from its use. Adjuvant therapy with tamoxifen should be considered in ER-positive DCIS, although conventional chemotherapy has not been found to be particularly effective. Neoadjuvant therapy and the use of trastuzumab for DCIS are currently under investigation and may be future treatment options for DCIS. Recurrences after treatment of DCIS are invasive 50% of the time. This underscores the importance of effective therapy and careful monitoring. The patient should be reassured that their chance of survival is excellent.

ACKNOWLEDGMENT
The authors thank Kathryn Carnes for her assistance.


