Ductal Carcinoma in Situ

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KEYWORDS
- Ductal carcinoma in situ
- Tamoxifen
- Mammography

KEY POINTS
- Management of ductal carcinoma in situ (DCIS) has evolved from radical surgery to the option of a more minimally invasive approach.
- Although some facets of care for DCIS have not had the benefit of direct prospective trial comparison, data demonstrate that breast conservation surgery performed with administration of radiotherapy, like mastectomy, is feasible and safe, despite the lack of consensus about what constitutes a negative margin.
- Because efforts to find a safe group for elimination of radiotherapy have resulted in data that conflict, radiotherapy still remains standard of care as a part of breast conservation for DCIS.
- Tamoxifen has also shown a significant recurrence benefit, both in the adjuvant treatment setting as well as the prophylactic setting for DCIS, and has become standard in the treatment of receptor-positive disease.

HISTORY
Ductal carcinoma in situ (DCIS), first termed intraductal, noninvasive, or noninfiltrating carcinoma, was originally treated similarly to invasive breast cancer. Even before mammography was routinely used, DCIS was known to show radiographic calcifications. Mammography was not so critical to the diagnosis of DCIS at that time, because most cases of DCIS presented as a palpable lesion that was most commonly of high-grade comedo histology. The other symptom commonly associated with DCIS (as well as invasive cancer) was bloody nipple discharge, and so this symptom was also considered an indication for diagnostic excision.

DCIS initially accounted for approximately 2% of all breast cancers detected. The incidence rates have markedly increased over the past several decades because of widespread implementation of screening mammography in the 1980s and 1990s, with the greatest increase in incidence for women older than 50 years. Although the rate of new cases of DCIS in younger women has continued to increase in the last decade, its incidence in women aged 50 years or older has stabilized since 1999,
and now accounts for 15% to 25% of detected lesions when enumerated by state, and, in 2011, accounted for 57,650 cases, or 20% of all breast cancers detected in the United States.\(^5\)

As with other cancers, the diagnosis of DCIS was achieved by excision before the era of the core needle biopsy. Similarly, for patients having bloody nipple discharge, a central duct excision was standard to establish a diagnosis, because the association with this symptom was recognized as early as the 1950s.\(^6\) Although local excision was standard for diagnosis of DCIS, the treatment of DCIS was more radical, and initially accomplished in a manner identical to that of invasive breast cancers. Although local therapeutic excision was occasionally performed, mastectomy was the primary treatment, via total, modified radical, radical, or extended radical mastectomy in more than 80% of cases\(^3\) with lymph nodes being removed, even although axillary nodal metastases were rarely found.\(^1\) Over the ensuing decades, the surgery varied widely, from bilateral mastectomy to local excision without radiotherapy.\(^7\)

**TERMINOLOGY AND HISTOLOGY**

**Histologic Classification**

The classification of DCIS has also evolved over the course of several decades as relationships between histologic variants have been clarified. The World Health Organization originally classified malignant breast disease as invasive or noninvasive, and solely divided noninvasive breast cancer into intraductal carcinoma and lobular carcinoma in situ (LCIS).\(^8\) Currently, noninvasive lesions are subclassified under several headings, with LCIS now part of the lobular neoplasia group, DCIS placed under a heading of intraductal proliferative lesions with hyperplasia and atypia, and intraductal papillary carcinomas now occupying a subheading of intraductal papillary neoplasms. DCIS with microscopic (≤1 mm) foci of invasion also occupy a separate classification of microinvasive carcinoma, and male breast lesions have also been separated into 1 category that includes both DCIS and invasive male breast cancer subtypes.\(^9\) Although this method of classifying DCIS lesions seems abstruse, there are fewer clinical management implications to this differentiation than the classification suggests. It is important for the practitioner to know that DCIS of most of these subtypes is treated similarly.

Some of the WHO classification change occurred because DCIS, relative to invasive ductal carcinoma, is not analogous to an LCIS relationship to invasive lobular carcinoma. DCIS and LCIS have similar names because historically LCIS was believed to be the precursor of infiltrating lobular carcinoma. Nonpleomorphic or usual-type LCIS is now known to be a marker for risk and not a cancer itself.

**DCIS and Invasive Cancer**

Although DCIS is a malignancy and staged by the American Joint Committee on Cancer as stage 0 breast cancer, the relationship between DCIS and invasive ductal cancer remains a subject of significant controversy, especially because not all DCIS progresses to invasive cancer. The Wellsing-Jensen model of evolution of breast cancer, proposed more than 3 decades ago,\(^10\) suggests that there is a progression from normal cells in the terminal duct lobular unit to cells having atypia. These atypical cells then progress to DCIS, which subsequently develops invasive capability. The Sontag-Axelrod theory of progression, proposed in a modeling study in 2005 based on clinical observations,\(^11\) suggests that DCIS is not a progenitor of infiltrating ductal cancer but instead evolves separately in a parallel pathway from a common progenitor.

Genetic alterations in DCIS of differing grades span a spectrum that is similar and analogous to the differences between grades of invasive cancer.\(^12,13\) In a variation
on the 2 models of breast cancer pathogenesis, others have more recently suggested that low-grade in situ lesions progress to low-grade invasive cancers, whereas high-grade in situ lesions progress to high-grade invasive lesions, although this has not been uniformly supported in studies of progression of breast cancer. Data from EORTC 10853 (European Organisation for Research and Treatment of Cancer 10853), randomizing patients having DCIS treated with breast conservation to radiotherapy or no radiotherapy, also showed that low-grade, intermediate-grade, and high-grade DCIS recurred as invasive disease at similar rates (9%–13%, \( P = .35 \)) at 10 years.

It is well established that the extent of DCIS correlates with the risk of invasion contained within the in situ lesion. Specifically, DCIS that spans a diameter larger than 5 cm has been found to have a markedly increased risk for the presence of occult invasive disease. This finding is clinically significant in the workup of patients having what is believed to be pure DCIS, because it suggested that, although DCIS lesion size is not critical for staging, the size of the lesion on diagnostic imaging may have prognostic implications for what is likely to be found on excision, and potentially, operative planning. Other such risk factors for invasion include palpable masses, high-grade histology, and cancerization of lobules, which refers to the intraductal spread of DCIS into the lobular unit and not invasion itself.

**Hormone Receptor Expression**

DCIS has been extensively characterized histologically, with perhaps the greatest volume of data present for estrogen receptors (ERs) and progesterone receptors (PRs). This area of study is important because of the prominent role that receptor expression plays in current treatment and its association with tumor response. One of the earliest extensive characterizations of ER expression in DCIS estimated the rate to be approximately 45%; however, the threshold to classify expression in this study was that 25% or more of cells had to stain for the receptor, higher than the current 1% threshold for ER (and PR) expression. In this same study, when the presence of any staining was used as the threshold, approximately two-thirds of lesions were considered positive. Subsequent determinations of receptors in DCIS were more consistent with this latter characterization, noting that approximately 65% expressed ERs when 5% to 10% staining is used as the threshold for positivity. Other studies note similar or slightly higher rates of ER expression, when 5% or less is used as the definition of ER-positive.

The receptor expression of DCIS also varies by grade, with approximately 75% of low-grade lesions expressing ER, whereas less than half of high-grade lesions do. This finding is consistent with differences seen by histologic subtype in which comedo-type DCIS is also more often negative for ERs and PRs than other variants. Although the grade and presence of comedonecrosis are predictors of receptor expression, the correlation is not strong enough to eliminate ER and PR staining in favor of using histology alone to determine whether hormonal therapy is appropriate.

DCIS lesions are also largely PR-positive at a slightly lower rate than for ER expression, at 60% to 70%. DCIS lesions, like invasive breast cancers, show a high correlation between ER and PR expression, with few lesions showing PR positivity when tumors are ER-negative, and lesions having 1 or both receptors positive at approximately 80%. Similar to ERs, as grade increases, PR expression declines in DCIS. Nevertheless, both are assayed, because lesions having either ER or PR expression are typically administered endocrine therapy because of the benefit it confers.
IMAGING EVALUATION OF DCIS

Mammography

Although several decades ago DCIS was largely diagnosed when found as a palpable abnormality, the routine use of screening mammography has increased the detection of DCIS and the percentage of cases of breast cancer that DCIS accounts for. The routine use of mammography began after dedicated mammography machines were introduced in 1969, and screen-film systems in 1972. This situation led to the Health Insurance Program of Greater New York study, which reported a 30% mortality reduction from mammography and the resulting Breast Cancer Detection Demonstration Project (BCDDP), which also evaluated mammography. The 20-year follow-up from the BCDDP reported a 93.9% to 98.2% 20-year adjusted survival rate for in situ lesions, dependent on age, with younger women having better survival. These studies set the stage for widespread use of mammographic screening for detection of invasive and in situ disease.

DCIS is detected in about 80% of cases by mammography, with more than 80% of those cases showing calcifications. Among all mammographically detected non-palpable breast cancers, 68% of calcifications are from DCIS, with these calcifications being associated with necrosis. Meanwhile, although DCIS less frequently presents as a palpable mass compared with several decades ago, 32% of mammographically detected nonpalpable masses with calcifications still represent DCIS, and 5% of masses that have no calcifications do also.

These data about presentation of DCIS are consistent with the notion that mammography is an efficacious screening modality for this disease. In 1 of the largest series of mammographically detected DCIS from the University of California San Francisco, 653,833 mammograms in 540,738 women performed in 1996 and 1997 from the National Cancer Institute’s Breast Cancer Surveillance Consortium were reviewed. The study reported that 1 in every 1300 mammograms led to a diagnosis of DCIS and 20.2% of all screen-detected breast cancers were DCIS, with the yield highest among women aged 40 to 49 years (28.2%, 95% confidence interval [CI] 23.9%–32.5%). Meanwhile, the sensitivity for DCIS detection by screening mammography was 86.0% (95% CI 83.2%–88.8%), compared with 75.1% for invasive breast cancers (95% CI 73.5%–76.8%). Sensitivity for DCIS detection did not differ by age, as it did for cases of invasive breast cancer (which increased with age), and the highest sensitivity for detecting DCIS was in women aged 40 to 49 years who had no previous mammogram (97.4%, 95% CI 85%–100%). The rates of nondetected DCIS were also markedly smaller than the incidence of screen-detected DCIS, supporting the conclusion that mammographic screening is 1 reason why the incidence and proportion of DCIS cases has increased.

Ultrasonography

Because of the predominance of screen-detected DCIS, with calcifications as the most frequent presentation, ultrasonography has played a minor role in the evaluation of DCIS. Ultrasonography has been investigated for, but has not been shown to be an effective screening modality, and outside its use for palpable abnormalities, does not have a role in either screening or evaluation of DCIS.

Breast Magnetic Resonance Imaging

Breast magnetic resonance imaging (MRI) is a highly sensitive imaging modality that detects occult foci of breast cancer not seen on mammography in 8% to 40% of cases. The ability of MRI to detect DCIS varies, dependent on the grade of the lesion.
In a large trial of 7319 women from Germany evaluating all women irrespective of risk and not just those presenting with an abnormality, mammography and MRI were both used for screening and compared. MRI showed no difference in sensitivity for low-grade DCIS when compared with mammography, but it had a higher sensitivity for intermediate-grade (31 vs 20%, \( P = .013 \)), and high-grade lesions (87% vs 46%, \( P < .0001 \)). With the approximate 95% 5-year to 10-year survival rate of DCIS detected without the benefit of MRI, and lack of data showing a survival advantage from breast MRI even for invasive cancer\(^{30,31} \) (with which there is greater room for survival improvement), it remains doubtful that breast MRI would be able to provide any survival benefit if added to routine screening of normal-risk patients for the detection of DCIS.

**NEEDLE BIOPSY**

*Fine-Needle Aspiration*

Needle biopsy of benign and malignant lesions has been in use since the 1930s,\(^ {32} \) although more widespread use for breast abnormalities did not begin until the 1970s.\(^ {33} \) Fine-needle aspiration (FNA), performed either by palpation or image guidance, allows examination of cells to assess the presence of malignancy as distinguished from hyperplasia and often from atypia.\(^ {34} \) The biopsy technique is convenient because it can be performed with a standard needle and syringe in the office, but it poses difficulty for the pathologist to determine whether a lesion is invasive or in situ even although attempts have been made to distinguish structural features in FNA specimens.\(^ {35-37} \) FNA is consequently less favored than core needle biopsy for establishing a cancer diagnosis, because the need to distinguish DCIS versus invasive breast cancer is critical to determine the proper treatment and operative plan.

*Core Needle Biopsy*

In contrast to FNA, core needle biopsy provides accurate assessment, with the benefit of providing architecture for histologic characterization and to distinguish invasive from in situ disease.\(^ {38} \) Core biopsy, whether by palpation, stereotaxis, or sonographic guidance, also frequently provides sufficient tissue for assessment of estrogen and PRs for pretreatment discussion of the role of antiestrogens in DCIS.

The more germane issue to a surgical practice that surgeons need to be aware of is that the use of core needle biopsy is associated with a low but significant rate of upstaging on final excision. Depending on the number of cores removed and the gauge of the core biopsy needle, complete excision of a lesion diagnosed by core biopsy as DCIS shows invasive cancer in approximately 10% to 20% of cases.\(^ {39,40} \) This finding is clinically most relevant in operative planning, because it relates to management of the axilla, as discussed later.

**SURGICAL AND RADIOTHERAPEUTIC MANAGEMENT OF THE BREAST**

*NSABP B-06*

The first National Surgical Adjuvant Breast and Bowel Project (NSABP) trial to be performed that had some impact on the surgical management of DCIS was a trial to assess surgical treatment of invasive breast cancer. In NSABP B-06,\(^ {41} \) lumpectomy, lumpectomy with radiotherapy, and mastectomy were compared, and 76 of the 2072 cases were retrospectively found on review to solely have DCIS with no invasive component. This small subset of patients was analyzed,\(^ {42} \) and the lumpectomy group without radiotherapy showed a 43% recurrence rate after an average follow-up of 83 months, with a 7% recurrence rate for lumpectomy with radiation. Although 1 of
the 27 patients having mastectomy died of her disease, none of the patients in that group was noted to have local recurrences. The numbers of patients in the 3 groups were all less than 30, and so these recurrence rates must be interpreted with caution, but the investigators concluded that breast conservation was feasible for DCIS, and further investigation was warranted.

**Breast Conservation**

Surgical treatment of DCIS dictates that patients undergoing wide excision have negative margins, with larger margins being better, because of a desire to limit recurrence rates. However, there is no consensus on what constitutes an appropriate margin in either DCIS or invasive breast cancer. In light of conflicting data, trials have had widely varying margin criteria, and outcome differences based on margin status have recently been called into question as a result of effective systemic chemotherapy and endocrine agents. The definition of a negative margin is therefore left to the discretion of the practitioner or institution.

Long-standing experience shows that even for patients with low-grade DCIS, elimination of radiotherapy may result in nearly one-third of patients experiencing a local recurrence, and some of these can occur well beyond 10 years postoperatively. Although mastectomy was the standard several decades ago, and although there is no large prospective randomized trial comparing breast conservation therapy (BCT) with mastectomy in DCIS as B-06 did for invasive breast cancer, patients have been reported to have low local recurrence and high survival rates with BCT, which includes breast conservation surgery in conjunction with radiotherapy; BCT is a standard treatment option for patients with DCIS.

Although there are innumerable small studies that have confirmed the need for radiotherapy in the setting of breast conservation for DCIS, there are 4 landmark prospective randomized trials that must be mentioned, evaluating radiotherapy for maximizing local control in DCIS. These trials are National Surgical Adjuvant Breast and Bowel Project (NSABP) B-17, European Organisation for Research and Treatment of Cancer (EORTC) 10853, SweDCIS, and the United Kingdom (UK), Australia, and New Zealand (UK/ANZ) trial. Two large retrospective series, the Collaborative Group Study, which reviewed patients having breast conservation and radiotherapy, and the retrospective series by Kerlikowske and colleagues, which evaluated lumpectomy alone, are of similar size and are also notable. Although each of these large retrospective series is different, they add consistent findings that have made radiotherapy standard of care in the setting of breast conservation for DCIS.

**NSABP B-17**

In 1993, the NSABP published results of a trial comparing lumpectomy with lumpectomy with postoperative radiotherapy (50 Gy) for localized DCIS. As breast conservation data started to accumulate for invasive breast cancer, patterns of operation for that disease began to change, leading to a paradox in how breast cancer was treated; invasive disease had local excision with radiotherapy as an option, whereas DCIS lesions still required mastectomy. This paradox prompted further investigation into the value of lumpectomy with or without radiotherapy. NSABP B-17 is considered a landmark trial investigating this paradigm.

There were 818 patients who had DCIS and lumpectomy who were randomized to no breast radiotherapy or radiotherapy at 50 Gy, beginning no later than 8 weeks postoperatively. In a long-term analysis at 207 months, ipsilateral breast recurrences occurred in 35% of the lumpectomy-only group and 19.8% in the group receiving radiotherapy. There was no difference between the arms in the incidence of
contralateral breast cancers. This trial, the first results of which were published in 1993, was the first to report the benefit of radiotherapy in this setting. The investigators concluded that lumpectomy and radiotherapy are more appropriate for DCIS than lumpectomy alone.

**EORTC 10853**

The EORTC performed a similar trial to evaluate the benefit of radiotherapy for women aged 70 years or younger having completely excised DCIS less than 5 cm without invasion or Paget disease. Axillary dissection was not recommended but, if performed, the axillary lymph nodes needed to be without metastases, and patients having compromised margins were permitted reexcision to negative margins. A total of 1002 patients were randomized to a radiotherapy dose of 50 Gy in 25 fractions within 5 weeks of surgery or no radiotherapy.

At a median follow-up of 10.5 years, the risk of local recurrence was reduced from 26% to 15% with the addition of radiotherapy. Recurrences were nearly evenly split between DCIS (103 patients) and invasive recurrences (106 patients). Contralateral breast cancers were not different in incidence or interval to contralateral breast cancer between the 2 arms. Multivariable model risk factors for recurrence included younger age (specifically, <40 years), detection because of symptoms, intermediately or poorly differentiated DCIS, solid or cribriform growth pattern, positive margins (although n was only 7), and treatment without radiotherapy.

**UK/ANZ Trial**

In 2003, the United Kingdom Coordinating Committee on Cancer Research DCIS Working Party began a trial to simultaneously evaluate the benefits of radiotherapy and tamoxifen in the setting of breast conservation for patients having locally excised DCIS. Based on the previously published results of NSABP B-17 and EORTC 10853, and concurrent to NSABP B-24 (later), which began accruing at the time, the trial was designed as a 2 x 2 factorial trial. The 1694 patients who entered the study were permitted to choose how they were randomized. One option was to undergo a complete 2 x 2 randomization to receipt of radiotherapy or not, and receipt of tamoxifen or not. Alternatively, these patients could choose to be randomized solely for the radiotherapy component or solely the tamoxifen component and openly select the other treatment option. There were 912 patients who chose to enter the complete 2 x 2 randomization, whereas 782 chose to be randomized to only 1 of the treatments, with 603 of these latter patients electing not to have radiotherapy (and thus being randomized to either tamoxifen or no tamoxifen).

Patients with unilateral or bilateral DCIS, who were believed to be amenable to breast conservation, were eligible. Two years after the start of the trial, inclusion criteria were amended to allow entry of patients with completely excised microinvasion less than 1 mm. Patients having positive margins and Paget disease were excluded, although reexcision to clear margins was permissible. Radiotherapy was administered as 50 Gy in 25 fractions over 5 weeks with no boost. Tamoxifen was administered at 20 mg daily for 5 years.

There were 1030 patients included in the radiotherapy analysis, with 58 developing a recurrence as DCIS and 60 developing a recurrence as invasive cancer. At a median follow-up of 4.4 years, the rate of recurrence in patients undergoing radiotherapy versus no radiotherapy was 7% versus 16% (P < .0001). Ipsilateral invasive events were reduced by 55% and ipsilateral DCIS by 64%, with contralateral events not affected by radiotherapy. These results again confirmed the findings of the NSABP and EORTC studies, albeit with a lower absolute recurrence rate than occurred in those trials.
**SweDCIS Trial**

The Swedish Breast Cancer Group began enrolling patients in a similar trial from 1987 to 1999, in which 1046 women were randomized to radiotherapy or no radiotherapy.\(^53,54\) Patients were eligible if they had DCIS and a clinically negative axilla. Patients having Paget disease, invasive carcinoma, or intracystic carcinoma in situ were excluded. Patients underwent local excision with or without 50 Gy of radiation administered in 25 fractions over 50 weeks, or 54 Gy in 2 series with a gap of 2 weeks, and 11% had microscopically positive margins, with 9% having a margin status unknown.

The absolute risk reduction for radiotherapy was 16% at 10 years, equally decreasing the risk of invasive and in situ events. Consistent with other trials, radiotherapy was more effective with older age, rising from a 6% risk reduction in the youngest to 18% in older patients. The investigators also attempted to find a low-risk group in whom radiotherapy could potentially be spared, but no such group could be found.

**Early Breast Cancer Trialists’ Collaborative Group Analysis**

In perhaps the most powerful assessment of the benefit afforded by radiotherapy, a meta-analysis by the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) (Oxford Overview)\(^55\) evaluated the 4 major DCIS trials having similar schema for patients having local excision randomized to either radiotherapy or no radiotherapy. These trials included the previously mentioned studies; NSABP B-17, EORTC 10853, SweDCIS, and the UK/ANZ Trial, for a total of 3729 patients evaluated after all exclusions, and a median follow-up of 8.9 woman-years.

Radiotherapy halved the rate of ipsilateral breast events, with a 5-year absolute reduction in risk of 10.5% (7.6% vs 18.1%), and a 10-year reduction of 15.2% (12.9% vs 18.1%). Overall, 24.8% of women had a breast event, and 74% of first events were in the ipsilateral breast. Recurrences were closely split between invasive and noninvasive types irrespective of whether radiotherapy was given, with 92 invasive and 100 noninvasive recurrences in those who had radiotherapy, and 204 invasive and 218 noninvasive recurrences in those who had excision alone. Among a small subset of 291 women within this analysis who did not receive radiotherapy because they were believed to be at low absolute risk of recurrence (negative margins and small low-grade DCIS), the 10-year risk of ipsilateral recurrence was 30.1% and highly significant, again confirming the benefit of radiotherapy, even in a presumably low-risk group.

**Notable Retrospective Series**

There are also 2 published studies that, although not prospective randomized trials, are notable because of their large size and focus on DCIS. The first evaluated patients who had lumpectomy and radiotherapy, and the second evaluated lumpectomy alone. The Collaborative Group Study retrospectively reviewed 1003 women having unilaterally mammographically detected DCIS who had BCT at 10 institutions throughout the United States, France, the Netherlands, and Canada.\(^26\) Patients were excluded if they had any physical examination findings, including a breast mass or bloody nipple discharge. This study also required that both breast-conserving surgery and radiotherapy for at least 40 Gy be performed, but margins varied from positive to greater than 2 mm, and no systemic chemotherapy or endocrine treatment was permissible. After a median follow-up of 8.5 years, the overall survival rate at 15 years was 89%, but the disease-specific survival at 15 years was 98% (95% CI 96%–99%). The local failure rate at 15 years was 16%, for invasive cancer and DCIS combined.

The second notable retrospective series is a study of 1036 women from the San Francisco Bay area, aged 40 years and older, treated by lumpectomy alone without
At a median follow-up of 77.9 months, 20.2% of the women experienced a recurrence. Compared with the Collaborative Group Study, which had a true local recurrence rate of invasive recurrences and DCIS recurrences of 3% and 2%, respectively, despite the lack of systemic endocrine therapy, the 5-year recurrence rates in this study for the analogous group (initial DCIS detected by mammography alone) was 6.6% and 14.1% at 5 years, respectively. Data from 2 such separate retrospective studies cannot technically be compared; however, the magnitudes of local failure rates in each of these studies corroborate the randomized trial data and are consistent with smaller series showing a benefit of radiotherapy.

MANAGEMENT OF THE AXILLA

Historically, patients having DCIS were treated identically to those having invasive breast cancer, with axillary lymph nodes routinely removed. Once sentinel node biopsy was being increasingly used for assessment of the axilla, DCIS was considered an appropriate clinical setting for its use, because of its feasibility and because even although the likelihood of metastatic disease was low, sentinel node biopsy removed fewer nodes, and efforts to incorporate immunohistochemistry to increase the sensitivity of nodal evaluation were ongoing. Studies have now shown that the rate of nodal metastases detected by hematoxylin and eosin staining for pure DCIS is only 1% to 2%. This low metastasis rate, controversial significance of immunohistochemically positive nodes, and 5-year survival of 95% even when nodes are not removed have called the value of sentinel node biopsy into question for DCIS. In an extensive review of the data, a panel from the National Cancer Institute found that the benefit did not outweigh the risks of the procedure and therefore did not recommend it for patients having DCIS. The specifics of DCIS with nodal metastases have also recently been investigated in a small series from Finland, which reported that most such metastases are isolated tumor cells or micrometastases, supporting the position that sentinel lymphadenectomy is not necessary in DCIS, because these findings suggest that it is unlikely to affect outcomes.

As noted earlier, patients having high-grade or comedo histology, or having DCIS lesions that span more than 5 cm, are significantly more likely to have invasion identified at complete excision. While sentinel node biopsy was becoming standard of care and indications were being refined, these criteria were considered an indication for sentinel lymphadenectomy in patients with DCIS. Some practitioners still perform sentinel node biopsy when lesions are high grade or more than 5 cm for patients having breast conservation. However, because sentinel lymphadenectomy can be performed accurately after lumpectomy, there is a trend to remove the sentinel nodes only if invasion is found on pathologic examination. Although another procedure may be necessary if invasion is found, it spares the patient the morbidity of nodal removal that may be unnecessary.

When considering DCIS lesions of all grades and sizes, patients having DCIS diagnosed by vacuum-assisted core needle biopsy have an upstaging rate on excision in 10% to 20% of cases depending on the needle gauge and the number of core needle biopsy samples. Because of this risk, although current practice does not routinely prescribe nodal evaluation for evaluation of DCIS, an exception is made for mastectomy patients, because removal of the breast precludes injection of the sentinel node dye, or at best, makes the accuracy of sentinel node biopsy uncertain. Sentinel lymphadenectomy is therefore performed in the setting of mastectomy, in case upstaging is found on pathologic examination of the breast specimen, so that unnecessary axillary dissection need not be performed.
EFFORTS TO ELIMINATE RADIOTHERAPY FOR DCIS

Van Nuys Prognostic Index

In 1995, Silverstein and colleagues\textsuperscript{61} created the Van Nuys classification, dividing DCIS by nuclear grade, and then those that were not high grade into lesions having or not having comedonecrosis. Thereafter, this classification was used in the Van Nuys Prognostic Index (VNPI),\textsuperscript{62} which was created to assist in determining which patients would have an unacceptable risk of local recurrence with BCT whether they received radiotherapy or not. The VNPI added tumor size and margin width to this classification to create a score of 1 to 3 (low risk to high risk) for each variable. The sum of these 3 variables created the overall score.

This classification was then modified to become the University of Southern California/Van Nuys Prognostic Index (USC/VNPI),\textsuperscript{63} by adding age to the other 3 variables in the model, because younger patients had been previously noted to have a higher risk for recurrence. This index now created a score ranging from 4 to 12, which was then stratified to predict who could undergo excision alone, who should undergo radiotherapy with local excision, and who required mastectomy. Recurrence in those with scores of 4, 5, and 6 did not benefit from the addition of radiotherapy, those with scores of 7, 8 or 9 received a 12\% to 15\% local control benefit from radiotherapy, and those having scores of 10, 11, or 12 had 5-year local recurrence rates of nearly 50\%, and were believed to require mastectomy.

Despite its apparent practical value, the application of the VNPI and USC/VNPI in clinical practice has remained controversial because of difficulties in reproducing the study results by other investigators.\textsuperscript{64–67} The validity also remains in question because the EBCTCG overview of the 4 large prospective DCIS radiotherapy trials showed that radiotherapy was effective in reducing ipsilateral recurrence irrespective of histologic or nuclear grade, the presence of comedonecrosis, or pathologic tumor size.\textsuperscript{55}

Eastern Cooperative Oncology Group 5194

A major prospective trial was launched by the Eastern Cooperative Oncology Group (ECOG) to determine if patients having low-grade or intermediate-grade DCIS could undergo local excision without irradiation.\textsuperscript{68} Patients having DCIS 2.5 cm or smaller of low or intermediate grade or DCIS 1 cm or smaller of high grade were eligible. Margins of at least 3 mm were required, and no residual calcifications on postoperative mammogram were permissible. At median follow-up of 6.2 years, the low-grade/intermediate-grade group comprising 565 patients had a 5-year rate of ipsilateral recurrence of 6.1\%, whereas at median follow-up of 6.7 years, the high-grade stratum, consisting of 105 patients, had a rate of 15.3\%. The investigators concluded that the low-grade/intermediate-grade group’s event rate was acceptable for omission of radiotherapy, unlike the high-grade group, but that additional follow-up is required to determine the long-term outcomes.

Twenty-One Gene Recurrence Score for DCIS

More recently, genome-directed efforts to determine who may eliminate radiotherapy after breast conservation for DCIS have been pursued. In 2011, data were presented\textsuperscript{69} from a trial to evaluate a modification of the 21-gene recurrence score used for determining risk of recurrence in the setting of invasive breast cancer. This study assessed whether this recurrence score, modified for DCIS to range from 0 to 100, might provide better assessment of who may be spared because of a low recurrence risk. This study evaluated 327 patients from ECOG 5194 having either low-grade or intermediate-grade DCIS 2.5 cm or smaller, or high-grade DCIS 1.0 cm or smaller. The DCIS
averaged 0.7 cm in size, and median follow-up was 8.8 years. The patients were arbi-
trarily divided into 3 groups based on their recurrence scores: less than 39 (low), 39 to
54 (intermediate), and 55 or more (high), and although the log rank \( P = .02 \) showed
that the overall curves differed between the groups, the confidence intervals for in-
breast recurrence risk between adjacent groups overlapped at 10 years (low 12.0%
[95% CI 8.1%–17.6%], intermediate 24.5% [95% CI 13.8%–41.1%], high 27.3%
[95% CI 15.2%–45.9%]). It therefore remains to be seen if the curves are becoming
similar or whether the number of patients at 10 years is too few to prevent widening
confidence intervals that suggest no statistical difference between the groups.

The study also evaluated 2 multivariable models for risk of in-breast recurrence.
Both models used tumor size and postmenopausal status, but 1 added the DCIS
score. Tumor size and postmenopausal status were significant in both models, with
the DCIS score also noted to be significant when added in \( P = .02 \). The results
suggest that the recurrence score may have some prognostic ability in determining
which patients may be able to be spared radiotherapy, although the study has not
yet been published and validation is required.

Although there may be promise in this gene profiling test, it is not known whether
this is more or less effective than the VNPI62 or the Memorial Sloan Kettering DCIS
nomogram.70 This subject is of particular importance in the era of cost containment,
because these latter 2 methods of assessment are free, in contrast to the expense
of running the 21-gene recurrence score for this purpose. It is hoped that further
studies will clarify its value and may allow radiotherapy to be omitted in patients
who will not benefit from its use.

**TAMOXIFEN**

**NSABP B-24**

After NSABP B-17, which established the benefit of radiotherapy with breast conser-
vation for DCIS, NSABP B-24 was designed to investigate tamoxifen in that setting.
Previous data had shown that tamoxifen reduced the risk of ipsilateral and contralat-
eral recurrences in patients with invasive breast cancer.71,72 NSABP B-24 was thus
created to randomize patients having breast-conserving surgery with radiotherapy
to subsequent tamoxifen or placebo.73

There were 1804 patients randomized who had DCIS and a life expectancy of at
least 10 years. Patients were excluded if their tumors showed invasion, although
LCIS could be seen along with the DCIS, and although axillary dissection was not rec-
ommended, patients having an axillary lymphadenectomy were excluded only if the
lymph nodes showed metastatic disease, indicating occult invasion. Radiotherapy
was standardized at 50 Gy, to be started no later than 8 weeks after surgery, even
although patients whose margins were microscopically positive were also not
excluded. Tamoxifen was administered in the treatment group at 10 mg twice daily
for 5 years, beginning within 56 days of surgery.

At a median follow-up of 74 months, the tamoxifen arm showed 37% fewer breast
cancer events overall, with 43% fewer invasive and 31% fewer noninvasive events.73
The results were further broken down to show that tamoxifen conferred a 38% reduction
in ipsilateral breast tumors in women younger than 50 years, and a 22% reduction in
those older than 50 years. Patients who were of younger age, had positive margins, or
had comedonecrosis were at significantly increased risk for recurrence. A more recent
analysis of the B-24 results74 noted a 15-year rate of invasive ipsilateral tumor recurrence
of 10% in the placebo arm and 8.5% in the tamoxifen arm, with 15-year contralateral
breast cancer incidence of 10.8% in the placebo arm and 7.3% in the tamoxifen arm.
NSABP B-24 therefore effectively established that tamoxifen provided both ipsilateral and contralateral benefit in patients undergoing breast conservation for DCIS. A retrospective subset analysis of patients from B-24, stratifying by receptor status, reported the benefit to be confined to receptor-positive DCIS, with a 10-year reduction of subsequent breast cancer events of 51% in ER-positive patients and no benefit from tamoxifen for ipsilateral or contralateral events in women with ER-negative DCIS. Because most DCIS lesions do show substantial ER and PR expression, tamoxifen has become a mainstay of treatment in this disease.

**UK/ANZ Trial**

As noted earlier, further suggestion of the benefit of tamoxifen was provided in the UK/ANZ trial, which evaluated the effects of radiotherapy and tamoxifen on DCIS undergoing local excision in a 2 × 2 design. Among 1576 patients randomly assigned to receive or not receive tamoxifen, ipsilateral events were 7% in the tamoxifen group and 10% in the no-tamoxifen group, which approached but did not reach significance ($P = .08$). Although there was no difference in rates of contralateral disease, when both ipsilateral and contralateral breast cancer events were combined, there was a significant difference in favor of the tamoxifen group (7% vs 11%, $P = .03$) having fewer events. When the patients with DCIS were subdivided further into those who received radiotherapy and those who did not, tamoxifen conferred no additional benefit in ipsilateral risk reduction in patients who received radiotherapy, but significantly lowered the risk of all events (ipsilateral and contralateral) from 10% to 6% ($P = .03$). This study did not include a subset analysis by ER status.

**NSABP B-35**

A trial is under way to assess the role of anastrazole compared with tamoxifen, among patients with ER-positive DCIS. The NSABP B-35 trial randomized women undergoing lumpectomy and radiotherapy to anastrazole or tamoxifen. This study is based on similar data suggesting a benefit for aromatase inhibitors in ER-positive invasive breast cancer and may provide another standard agent for use in DCIS. Analysis is expected in 2014.

**HUMAN EPIDERMAL GROWTH FACTOR 2 (HER2/neu)**

One of the most clinically relevant histologic assessments performed for invasive breast cancer is assessment of HER2/neu expression. Amplification or overexpression of this gene has been correlated with poor prognosis in invasive breast cancer. In studies of pure DCIS, 66% of lesions are found to overexpress HER2, and although more frequently found in ER-negative or PR-negative DCIS than in ER-positive or PR-positive DCIS, overexpression of HER2 does not correlate with a difference in response to endocrine treatment among receptor-positive lesions.

Trastuzumab is a monoclonal antibody that binds to the HER2/neu receptor. Because adjuvant trastuzumab with chemotherapy results in a survival benefit for women with HER2-positive invasive breast cancer, and because it has been shown to act as a radiosensitizer in other malignancies, its use is being investigated in DCIS.

**NSABP B-43**

The NSABP B-43 trial will investigate the potential for trastuzumab to decrease local recurrence rates in DCIS. This is a phase III trial, which randomizes women with HER2-positive DCIS undergoing lumpectomy and radiotherapy to administration or...
PREVENTION

**NSABP P-1**

The definitive trial for prevention of both DCIS and invasive breast cancer is the NSABP P-1 trial, in which 13,388 women were randomized to receive a placebo or 20 mg of tamoxifen daily for 5 years. Patients were eligible for the trial if they were older than 60 years, or between 35 and 59 years with a 1.66% or greater 5-year risk of breast cancer as calculated by the Gail model, or a had a history of LCIS. The results showed that in addition to the reduction in the risk of invasive cancer, there was a 50% reduction in the annual risk of in situ disease from 2.68 to 1.35 per 1000 women. It was concluded that tamoxifen was an effective preventative agent for women of increased risk, lowering the risk of DCIS and invasive cancer, and that women with DCIS specifically should receive tamoxifen because they have at least as high a risk of developing invasive breast cancer as women with a history of LCIS, for whom the agent showed efficacy in preventing breast cancer.

**STAR Trial**

The other landmark prevention trial, known as NSABP P-2, or the STAR (Study of Tamoxifen and Raloxifene) trial assessed the relative preventative value and safety of raloxifene and tamoxifen for developing invasive and noninvasive breast cancer, uterine cancer, bone fractures, and thromboembolic events. There were 19,747 postmenopausal women with an increased 5-year risk of breast cancer similar to the P-1 trial, who were randomized to either 20 mg of daily oral tamoxifen or 60 mg of daily oral raloxifene over 5 years. The trial reported an equal effect between tamoxifen and raloxifene on invasive breast cancer and none of the high-risk subsets (eg, those with atypia, a history of LCIS, increased risk according to the Gail model) were found to have differences between tamoxifen and raloxifene. However, the DCIS findings reported fewer noninvasive lesions, including both LCIS and DCIS in the tamoxifen subgroup relative to raloxifene. This finding did not reach statistical significance, but an update of the trial has found persistence of this trend. In the updated results after 81 months of median follow-up, raloxifene was found to be only 78% as effective as tamoxifen in preventing all noninvasive lesions, with the difference between the agents confined to DCIS or cases of mixed DCIS and LCIS. It was also 76% as effective for prevention of invasive cancer; however, raloxifene does have an advantage of a significantly lower risk of endometrial cancer, and no difference for other invasive cancers, events related to ischemic heart disease, or stroke.

**SUMMARY**

Management of DCIS has evolved from radical surgery to the option of a more minimally invasive approach. Although some facets of care for DCIS have not had the benefit of direct prospective trial comparison, data show that breast conservation surgery performed with administration of radiotherapy, like mastectomy, is feasible and safe, despite the lack of consensus about what constitutes a negative margin. As efforts to find a safe group for elimination of radiotherapy have resulted in data that conflict, radiotherapy still remains standard of care as a part of breast conservation for DCIS. Tamoxifen has also shown a significant recurrence benefit, both in the adjuvant treatment setting as well as in the prophylactic setting for DCIS, and has no administration of 2 doses of trastuzumab 3 weeks apart. Patients who are ER-positive or PR-positive will also receive endocrine therapy.
become standard in the treatment of receptor-positive disease. Investigation of other agents that are of benefit for invasive breast cancer and show preliminary promise in DCIS, such as anastrazole and trastuzumab, is ongoing.

REFERENCES


