Management of ductal carcinoma in situ (DCIS) commonly involves excision, radiotherapy, and hormonal therapy. Radiotherapy is employed for local control in breast conservation. Evidence is evolving for several radiotherapy techniques exist beyond standard whole-breast irradiation.

Summary of Literature Review

Introduction

Ductal carcinoma in situ (DCIS; intraductal carcinoma) is a noninvasive breast cancer originating from the cells that line the mammary ducts. The term encompasses a broad range of diseases, ranging from low-grade, indolent lesions to high-grade, aggressive tumors that can be a precursor to invasive disease. Patients with DCIS can be asymptomatic at the time of presentation (radiographic findings on mammogram) or present with symptoms such as a palpable mass or nipple discharge. The incidence of DCIS has markedly increased in the past decade, primarily due to improvements in screening utilization and imaging techniques. This has led to a shift in disease presentation from years past, when patients with DCIS had symptomatic findings, to the current era, in which these lesions are most commonly detected solely in the process of evaluating abnormal mammographic findings.

Pathologically, DCIS is defined by the presence of malignant epithelial cells within the well-defined breast ducts. The malignant cells are, by definition, bound by an intact basement membrane without any basal myoepithelial layer invasion. There are several architectural subtypes of DCIS: solid, comedo, micropapillary, papillary, and cribriform. Furthermore, DCIS is classified qualitatively by nuclear grade (high, intermediate, and low, based on cytologic/structural features) and the presence or absence of necrosis.[1,2] Often, patients with DCIS have lesions that contain at least two architectural subtypes. Although pathologic criteria have been established to distinguish DCIS from normal hyperplasia and atypical ductal hyperplasia (ADH), the diagnosis can still be very challenging for pathologists, as these entities represent a continuum of cellular and architectural atypia. Distinguishing between ADH and DCIS can be particularly difficult, as demonstrated by significant differences in diagnosis on expert pathology review.[3,4]

There are three general treatment approaches for women with DCIS: 1) mastectomy; 2) breast-conserving surgery (BCS) alone, encompassing wide local excision, lumpectomy, quadrantectomy, and partial mastectomy; and 3) BCS followed by radiation therapy, classically defined as breast conservation therapy (BCT). Historically, mastectomy was the standard treatment for this disease. Over the last 2 decades, the treatment has shifted to a breast-conserving approach (ie, lumpectomy with or without definitive breast irradiation) for patients with DCIS localized to one quadrant, if the disease is resectable with acceptable cosmesis. The standard radiation treatment has used conventionally fractionated, whole-breast radiation, delivered daily over 5 to 7 weeks. In more recent years, there has been a resurgence of two accelerated regimens for both DCIS and invasive breast cancers: 1) accelerated partial-breast irradiation (PBI), which delivers biologically equivalent doses of radiation to only a portion of the breast for a shorter period (typically ≤ 5 days); and 2) hypofractionated whole-breast radiation therapy performed over approximately 3 weeks. The management of DCIS remains controversial for several reasons. Although there are no randomized trials comparing BCT with mastectomy for DCIS, comparisons of BCT with historic mastectomy controls have suggested no difference in overall survival. In terms of breast conservation, there are four published randomized trials for DCIS, evaluating the benefit of adjuvant
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whole-breast radiation after local excision: the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-17 trial[5,6]; the European Organisation for Research and Treatment of Cancer (EORTC) 10853 trial[7]; the United Kingdom/Australia/New Zealand (UK/ANZ) cooperative trial[8]; and the Swedish trial[9]. All suggested a benefit in local control with the addition of whole-breast radiation compared with lumpectomy alone (with or without tamoxifen).

Because of the heterogeneity of DCIS, it is unclear whether all patients with DCIS uniformly benefit from treatment. Although it appears, based on retrospective series, that there is an increased propensity for local recurrence after BCT for comedo histologies, high-grade lesions, close/positive surgical margins, and younger patients, there is a paucity of complete data on these prognostic factors. The limited existing randomized DCIS studies do not adequately address the relative impact of these various factors in a prospective manner, nor do they address whether a subgroup of patients with low-risk DCIS has a small enough potential benefit from radiation that it may be deferred. Thus, it is unclear how to factor all of the possible clinical and pathologic elements into the decision-making process. Additional prospective studies incorporating these variables into therapeutic interventions are required before they can be routinely used to guide treatment decisions. Moreover, the existing randomized data had assessed the benefit of adjuvant whole-breast radiation after local excision, but a more recent trend toward PBI has not been adequately studied. The existing literature on PBI for DCIS consists mainly of retrospective analyses with relatively short follow-up.

Additionally confounding the data, the proportion of patients with DCIS detected by physical findings and symptoms has decreased significantly with the increased use of screening mammography. Thus, the earlier literature reporting on clinically symptomatic DCIS patients is not directly applicable to and cannot be used to guide decision making for patients diagnosed in the current era in which the vast majority have subclinical disease at presentation that is subsequently detected, mainly by mammography. It is now more apparent that the variations in clinical and pathologic presentations of DCIS subtypes and the differences in their natural histories suggest that DCIS is not one entity, but rather a spectrum of diseases that ultimately may require different management approaches. Unfortunately, there are insufficient long-term data assessing the efficacies of the various treatment modalities for the different subtypes of DCIS. Lastly, there is a paucity of data on the natural history of DCIS in the untreated patient.

More recently, the addition of tamoxifen has been shown to help prevent recurrence of ipsilateral breast cancer in some groups of DCIS patients. The use of tamoxifen as a therapeutic option after BCS (with or without radiation) has added to the complexity of therapeutic decision making but must be considered in hormone receptor–positive DCIS patients as a means of decreasing in-breast recurrence. Complicating treatment considerations further, tamoxifen is also beneficial in reducing contralateral breast cancers. The role of aromatase inhibitors for DCIS is under active investigation. Since the focus of this article is on local treatment, management, and prevention of local relapse, tamoxifen and other anti-endocrine agents will be discussed below as they relate to or affect local treatment choices.

Several ongoing randomized trials are attempting to address many important local and systemic therapies for DCIS: the Radiation Therapy Oncology Group (RTOG) 1005 trial[10], the NSABP B-43 trial[11], the Trans Tasman Radiation Oncology Group (TROG) 07.01 trial[12], and the French multicentric BONBIS trial[13].

Local Treatment Variables

Mastectomy

Many reasons have been cited to justify the use of mastectomy as the initial treatment of intraductal carcinoma. First, the rate of occult multicentricity found in mastectomy specimens is approximately 20% to 30%. This rate, however, may be decreasing, as tumors are being detected earlier with wider use of screening mammography. Second, the rate of occult invasive disease found in mastectomy specimens is approximately 10%. Third, residual normal breast tissue left in the patient after BCS might undergo malignant transformation over time; mastectomy essentially eliminates this possibility. Fourth, there is a significant risk of invasive recurrence after BCT, and invasive cancers are theoretically more life-threatening than DCIS. Lastly, mastectomy series consistently provide the highest relapse-free survival rates of any treatment approach, albeit without improvement in disease-free or overall survival.

The reported outcomes after treatment with mastectomy show survival rates of 96% to 100%. Local-regional control rates are also reported as 96% to 100%. However, survival and
local-regional results are virtually always reported using crude outcome calculations. The lack of actuarial outcome analyses for mastectomy series is a serious impediment to comparison with breast conservation series, which have typically been reported with actuarial outcome calculations. Although the recent emphasis on the treatment of DCIS has focused on BCT instead of mastectomy, no prospective randomized trials have included a mastectomy arm to date (mainly due to the number of patients that would be required to test for a potential survival advantage of 1% to 3% over BCT, which would be so large that accruing patients would not be feasible). Furthermore, it would be difficult, if not impossible, to convince the needed number of women to agree to randomization between two such drastically different local therapies in contemporary practice. Therefore, the absence of a mastectomy arm in current prospective randomized trials will preclude the definitive comparison of mastectomy with BCT.

Although breast-conserving approaches have replaced mastectomy for DCIS in most cases, there are a few instances in which a mastectomy may be indicated. These include multicentric DCIS, unattainable negative margins, patient choice, large tumor size relative to small breast size, diffuse microcalcifications on imaging studies, and DCIS associated with BRCA mutation (in which patients may opt for bilateral mastectomies). For a discussion on the use of postmastectomy chest wall irradiation in cases of pure DCIS, please see the ACR Appropriateness Criteria® Postmastectomy Radiotherapy[16] (see Variant 1 and Variant 2).

Breast conservation approaches

The components of treatment that need to be considered in a DCIS patient motivated to receive breast conservation can be divided into three major categories:

1. BCS to remove all disease and suspicious calcifications and to achieve a negative surgical margin.
2. Adjuvant radiation therapy, used to further decrease local relapse after BCS. This can be divided into three delivery methods:
   • Standard conventionally fractionated whole-breast radiation (delivered daily over 5 weeks with or without boost);
   • Accelerated PBI, in which a limited portion of the breast at highest risk for local recurrence is radiated in a shorter course, typically ≤ 5 days;
   • Accelerated hypofractionated whole breast radiation, in which the whole breast is radiated with higher daily fraction size for a shorter overall treatment time of approximately 3 weeks.

The following will review data on the radiation delivered with conventionally fractionated, whole-breast treatment for DCIS. The data on accelerated PBI and hypofractionated whole-breast radiation therapy as they pertain to DCIS will be discussed in a separate section in this guideline.

3. Tamoxifen for 5 years in hormone receptor–positive DCIS (used in a few of the randomized trials) to further reduce in-breast recurrence rates.

Although the addition of both radiotherapy and tamoxifen have been shown to independently improve local control in prospective randomized studies, the question remains whether subsets of DCIS patients have limited benefit and can forgo these adjuvant treatments, since neither confers a survival benefit.

Breast-conserving surgery followed by radiotherapy

Single-institution data on patients treated with surgical excision followed by radiation therapy have demonstrated breast failure rates of 16% to 18% at 20 years.[17,18] Solin et al[19] updated the largest multi-institutional experience of DCIS and reported a 15-year actuarial local failure rate of 19%. Subset analyses demonstrated local failure rates of ≤ 8% for patients with negative margins or age ≥ 50 years. The cause-specific survival rate for these conservatively managed patients was an excellent 98% at 15 years, which is comparable to the results of mastectomy series.

Re-evaluation of the pathologic material from the NSABP B-06 trial (a randomized trial evaluating postlumpectomy breast radiation for invasive breast cancer) revealed that 76 patients had in situ rather than invasive breast cancer.[14] Local failure rates for the patients treated with excision vs excision followed by radiation therapy were 43% and 7%, respectively, at a mean follow-up interval of 83 months.[14]

As previously mentioned, four prospective randomized trials have been published to date comparing excision alone with excision followed by radiation therapy (with or without tamoxifen). A fifth trial has not yet been published, but the data have been presented. All trials treated the whole breast to 50 Gy in 5 weeks without the use of a boost. The first trial, the NSABP B-17 trial, had the longest follow-up, at 20 years. It randomized patients after lumpectomy to radiation vs no radiation (tamoxifen was not used) and demonstrated that local failure was reduced from a crude rate of 35%
without radiation to 19.8% with radiation. [20] The inclusion criteria for this study were localized DCIS of any histology detected either clinically or mammographically, with negative margins following excision (defined as no tumor cells on the inked resection margin). The 12-year data revealed that radiation therapy resulted in a greater reduction in the incidence of invasive recurrences, the potentially life-threatening form of recurrence (relative risk [RR] = 0.38; \( P < .00001 \)), but also significantly reduced noninvasive recurrences (RR = 0.49; \( P = .001 \)). Local failure was significantly increased for patients with questionable or positive surgical margins and for those with marked to moderate comedo necrosis. [6]

The EORTC 10853 trial randomized DCIS patients after lumpectomy to radiation vs no radiation without the use of tamoxifen. In the 15-year update, the risk of any local recurrence was reduced by 48% with the addition of radiotherapy. The 15-year local recurrence-free rate was increased from 69% with excision alone to 82% with the addition of breast radiation \( (P < .001) \). No differences for breast cancer-specific survival or overall survival were observed. [7] The risk of recurrence was greatest in the first 5 years after treatment, with hazard rates of 4.0% per year after excision alone vs 2.0% per year with the addition of radiotherapy. These rates decreased to 2.0% and 1.2% in the second 5 years, and to 1.3% and 0.6% after that.

Similar to the long-term outcomes in the B-17 trial, radiation therapy significantly reduced invasive and DCIS recurrences in this trial. Factors that predicted an increase in local recurrence on multivariate analysis included age \( \leq 40 \) years, palpable DCIS lesions, involved surgical margins, cribriform and solid histologic subtypes, and treatment with lumpectomy only. [7]

The UK/ANZ DCIS randomized trial had a more complex design in which, after study enrollment, patients were entered into a modified 2 × 2 randomization of with or without radiation therapy and with or without tamoxifen, or elect randomization to only with or without radiation therapy or with or without tamoxifen. [8] Notwithstanding the complexity of the study design, the published results (median follow-up of 12.7 years) demonstrated a reduction in ipsilateral breast cancer recurrence rates with the addition of radiotherapy (19.4% vs 7.1%; \( P < .0001 \)).

A phase III trial originating from Sweden, the SweDCIS trial, [9] also demonstrated a benefit from adjuvant radiation. At a mean follow-up of 8 years, the cumulative incidence of ipsilateral breast events in the radiation arm (12.1%) was comparably less than that of the observation arm (27.1%), with a corresponding RR of 0.40 (95% confidence interval [CI], 0.30–0.54). A notable difference between this protocol and the aforementioned trials was that this study did not require microscopically negative margins prior to radiation; 10% of the patients had positive surgical margins in this study.

Data from these four trials were pooled in a meta-analysis performed by the Early Breast Cancer Trialists Collaborative Group. [21] The 10-year risk reduction for any ipsilateral breast event was 15.2% (12.9% vs 28.1%; \( P < .00001 \)); effectiveness was significant regardless of risk factors such as age, grade, margin status, detection method, tumor size, presence of comedo necrosis, or use of tamoxifen. As with the individual trials, no difference in overall survival was observed.

The results of the RTOG 98-04 trial were recently presented at two national meetings and have appeared in abstract form. [22, 23] This phase III randomization trial specifically examined the benefit of radiotherapy after excision in “favorable” DCIS cases (asymptomatic, grade 1–2, size \( \leq 2.5 \) cm, and margins \( \geq 3 \) mm). Although the trial closed early due to low accrual, the 7-year recurrence rates were 6.7% without radiotherapy vs 0.9% with radiotherapy \( (P = .0003) \), corresponding to a hazard ratio of 0.11. Of note, although the majority of patients were treated with standard fractionation, 8.4% of those enrolled received a hypofractionated whole-breast regimen. This trial reinforces the idea that all patients with DCIS (even those with favorable clinical and pathologic features) will have a lower chance of local recurrence with postlumpectomy radiation. However, the magnitude of this benefit may be small in a favorable subset, such that some patients and physicians may consider the benefit not of clinical significance.

In summary, all five of these prospective randomized trials have consistently demonstrated a significant improvement in local control with the use of adjuvant radiation therapy, with a risk reduction of > 50% in both invasive and in situ ipsilateral breast tumor recurrence rates, with no difference in overall survival (these studies were not powered to detect a survival difference).

**Excision alone**

The primary criticism of the currently published randomized DCIS trials is the lack of stratification before randomization by tumor grade, histology, or size, because such stratification might have identified a subset of patients who could have been adequately treated with excision alone. Selected
patients have been managed with excision alone in retrospective studies.[24] The criteria for consideration of excision alone in these studies were similar: lesions detected mammographically, without a palpable component, measuring ≤ 25 mm, and with negative margins following excision. Local failure rates were reported to be 10% to 15%, comparable to single-institution reports of surgical excision followed by radiation therapy in less rigorously selected patients. These series also noted that most of the breast failures were in patients with tumors of the comedo subtype, those with inadequate margins, and young patients. For patients treated with lumpectomy alone, Silverstein et al.[24] reported that the risk of local recurrence was reduced with increasingly wide negative margins of resection.

The Van Nuys Prognostic Index, adopted from a review in which a risk category was developed based on margin status, histologic subtype, tumor size, and patient age, using a cohort of DCIS patients treated at two institutions,[25] continues to be used by some practitioners as part of their decision-making process for adjuvant radiation therapy after local excision. It is important to note that the data from this “scoring system” were derived from retrospective data and that all prospective randomized data published to date have consistently demonstrated an improvement in local control in all patients.

Other groups have attempted to identify subgroups of DCIS patients, using a prospective study design, who may have minimal benefit from radiotherapy. A single-arm protocol of highly selected patients with small low-grade DCIS treated with BCS with widely negative margins of ≥ 1 cm was initiated in Boston but was closed early due to the high number of local recurrences with observation alone.[26] The previously discussed RTOG 98-04 trial, which was designed to assess the outcomes of observed vs radiated low-risk DCIS patients after BCS, did show a local control benefit to radiotherapy, although it was closed prematurely due to lack of accrual.

The Eastern Cooperative Oncology Group (ECOG) initiated a prospective single-arm trial (E5194) of observation for low-risk and intermediate-risk DCIS.[27] The two cohorts in this study included the low-risk group, defined as low-grade or intermediate-grade DCIS measuring ≤ 10 mm; and the intermediate-risk group, defined as high-grade DCIS measuring ≤ 10 mm with negative margin widths of ≥ 3 mm. It is notable that the average tumor sizes for the low-risk and intermediate-risk cohorts were only 6 mm and 5 mm (when enrollment guidelines allowed for ≤ 25 mm and ≤ 10 mm, respectively), suggesting that the patients enrolled in this trial were highly selected, with tumors significantly smaller than permitted by the protocol eligibility criteria. With a median follow-up of 6.7 years for the low-risk group and 6.2 years for the intermediate-risk group, the 5-year ipsilateral breast relapse rates were 6.1% and 15.3%, respectively; at 7 years these increased to 10.5% and 18.0%. Given the long natural history of DCIS, often with late recurrences (beyond 10 years), particularly for low-grade and intermediate-grade DCIS, these data are considered early results and longer follow-up is required. Interestingly, researchers at two institutions recently published the combined outcomes over a 29-year interval of 263 patients from their hospitals who were treated with excision and whole-breast radiotherapy who would have met the entry criteria for E5194. They found a more than 70% lower local recurrence rate at 5 years compared with excision alone in E5194 for both low-risk (1.5% vs 6.1%) and high-risk groups (2% vs 15.3%).[28]

A subsequent analysis of the E5194 cohort applied a 12-gene assay to validate a derived recurrence risk score (the 12-gene Oncotype DX DCIS score) to predict for whom radiotherapy would be of minimal benefit. Further validation is necessary before this genetic profile is routinely used in clinical decision making[29] (see Variant 3 and Variant 4).

**Systemic therapy**

Because DCIS is a process confined within the ductal system of the breast, it has no potential to spread to distant body sites. Thus, there is no need to deliver any therapy that would treat the patient “systemically” (ie, with chemotherapy or anti-endocrine therapy to treat organs beyond the breast). However, BCT has been improved (yet made more complex) by the recent appreciation that anti-endocrine therapy (using tamoxifen) impacts local control in the breast conservation setting. Results of the NSABP B-24 trial demonstrated that the addition of tamoxifen to postlumpectomy breast radiotherapy for DCIS significantly reduced ipsilateral breast tumor recurrences (RR = 0.60; 95% CI, 0.38–0.96) but did not have an impact on survival.[30] Further progress was made when Allred et al.[31] analyzed subsets of patients treated in the NSABP B-24 trial and found that the benefit in local control with tamoxifen was associated only with patients who had estrogen receptor (ER)-positive disease. As a result, all DCIS lesions should routinely undergo hormone receptor status assessment prior to consideration of eligibility for tamoxifen. The role of tamoxifen in the setting of
DCIS treated with mastectomy has not been determined to date.

Wapnir et al.[20] analyzed data from 2,615 women with primary DCIS who participated in the NSABP B-17 and B-24 trials for ipsilateral breast tumor recurrence; patients were followed for a median of 207 months in B-17 and 163 months in B-24. Ipsilateral breast tumor recurrence was a first failure in 490 patients (263 invasive, 227 noninvasive). The 15-year cumulative incidence of all such recurrences was 35% for lumpectomy only and 19.8% for lumpectomy with whole-breast irradiation in B-17. In the B-24 trial, the incidence was 16.6% for lumpectomy with whole-breast irradiation plus placebo and 13.2% for lumpectomy with whole-breast irradiation plus tamoxifen.

Currently, there are no published phase III data on the use of aromatase inhibitors for DCIS. Both NSABP B-35 (http://www.nsabp.pitt.edu/NSABP_Protocol_Chart.pdf) and International Breast Cancer Intervention Study (IBIS)-II DCIS (http://www.ibis-trials.org/thetrials/ibistrials/ibis-2-dcis) have completed accrual in the comparison of anastrozole vs tamoxifen as adjuvant therapy for DCIS. Because DCIS expresses human epidermal growth factor receptor 2 (HER2/neu) more often than invasive cancers,[32] the benefit of trastuzumab for HER2/neu-positive DCIS is being evaluated in the phase III NSABP B-43 trial,[11] in which patients will receive 6 weeks of whole-breast irradiation and be randomized to 2 cycles of trastuzumab delivered concurrently with radiation vs no systemic therapy (see Variant 3 and Variant 4).

The Role of Surgical Assessment of the Axilla in DCIS

There is currently no role for axillary dissection in the management of DCIS, even for high-grade or comedo lesions, because in theory pure DCIS is pre-invasive and should not metastasize. Although the risk of axillary involvement for pure DCIS approaches 0% in contemporary studies,[19] the preoperative diagnosis of DCIS by core needle biopsy is upstaged after the definitive procedure in as many as 9% to 15% of patients,[33,34] requiring these patients to subsequently undergo a separate second surgical procedure to evaluate the axilla. Furthermore, contemporary series suggest that there is a difference in lymph node involvement for patients with DCIS diagnosed at biopsy (10% node-positive) vs pure DCIS after definitive surgery (5% node-positive),[35,36] as well as for DCIS with microinvasion (9% node-positive) vs pure DCIS (5% node-positive).[37,38]

These contemporary series use the sentinel lymph node biopsy (SLNB) procedure to assess the axillary nodal status in lieu of a full axillary dissection, thus diminishing the morbidity of surgical evaluation of the axilla while preserving the accuracy of surgical nodal evaluation. As a consequence, there is renewed discussion as to the appropriateness of surgical evaluation of the axilla for DCIS using SLNB to identify patients at increased risk for nodal involvement, in order to prevent an additional delayed procedure after definitive local surgery. From the more detailed histopathologic evaluation of lymph nodes removed with SLNB compared with axillary dissection, reports of positive SLNBs have been described in up to 12% of cases of DCIS,[39,40] but the clinical relevance of a positive SLNB in the setting of pure DCIS has yet to be demonstrated.[41] Currently, the few studies reporting the impact of SLNB on DCIS patients is limited mainly to single-institution series, and it remains particularly unclear how micrometastasis or isolated tumor cells in lymph nodes affect outcomes or should influence management.[42]

As a result, although SLNB is not a routine component of breast-conserving surgical management of most patients with DCIS, it is used in specific situations. For example, in patients undergoing mastectomy with the preoperative diagnosis of DCIS, an SLNB is often advocated due to the greater than 10% risk of occult invasive disease in the mastectomy specimen and the greater than 10% sentinel node positivity.[43] If SLNB is not performed at the time of mastectomy, the ability to perform an SLNB procedure subsequent to mastectomy is precluded, with delayed complete axillary dissection as the only option for surgical evaluation of the axilla. In DCIS patients with radiographic evidence of extensive disease or tumor size measuring > 2.5 cm, SLNB may also be considered, as the risk of nodal involvement appears to rise with increased size of DCIS.[34]

Microinvasive Disease (DCIS With Microinvasion)

Microinvasive carcinoma (DCIS with microinvasion) is pathologically defined by the presence of early and minimal penetration of the duct wall by cancer cells beyond the basement membrane as seen by conventional light microscopic evaluation.[44] Although special staining can be used to demonstrate the absence of a myoepithelial layer surrounding the tumor cells to define a tumor that has invaded beyond the confines of a duct, there remains some controversy as to the exact
definition of microinvasion for DCIS, due to variations in the quantitative definitions. Many publications use the criteria of ≤ 2 mm of invasion,[45] whereas the staging system from the American Joint Committee on Cancer (AJCC) specifically defines microinvasion as ≤ 0.1 cm (T1mic).

The presence of unequivocal invasion is required for the diagnosis; cases with equivocal invasion should not be considered microinvasion. Cases with > 2 mm of invasion are sometimes regarded as demonstrating “minimal invasion” but should be distinguished from microinvasion (T1mic) as an invasive cancer (T1a).

Limited information has been reported regarding treatment outcomes for microinvasive carcinoma of the breast as a separate entity. Typically, DCIS with microinvasion cases are included with early-stage invasive disease (eg, T1a lesions).[45] Thus, there are limited data on DCIS with microinvasion, although the actual diagnosis of microinvasive carcinoma is increasing due to improved early detection. No randomized trials have evaluated therapy for microinvasive disease. Modern single-institution series do not indicate a worse outcome for DCIS with microinvasion relative to that of comparable cases of high-grade DCIS.[46,47]

For regional nodal management, microinvasive carcinoma carries a small but real risk of axillary lymph node metastasis, with nodal involvement ranging from 3% to 10%, although higher and lower risks have been reported.[45] With the development of SLNB techniques, the decision to evaluate the axilla surgically is a less difficult one, given the reduced morbidity of the procedure compared with axillary dissection and the large impact that a positive lymph node would potentially have on systemic management of a patient with a microinvasive primary tumor. Many clinicians now include pathologic axillary staging (eg, with an SLNB) as a standard part of surgical management of this disease.[40]

The major difference in the local management of DCIS with microinvasion compared with management of pure DCIS is that lumpectomy alone is not considered a standard option for microinvasive carcinoma of the breast. The possible exception to this caveat would be in the setting of an ER-positive microinvasive tumor in a postmenopausal “elderly” woman following lumpectomy who would be receiving adjuvant hormonal therapy. In the Cancer and Leukemia Group B (CALGB) randomized trial of lumpectomy followed by tamoxifen alone vs tamoxifen and radiation for women aged ≥ 70 years with T1 tumors (which presumably included but did not specifically evaluate those with microinvasive disease), the recent update showed only a modest benefit with the use of radiation (breast relapse–free survival rates of 98% vs 91% at 10 years).[48] Although the existing data on DCIS with microinvasion are retrospective, involving small numbers of patients,[47,49,50] a recent relatively large, single-institution series reported long-term outcomes of pure DCIS compared with microinvasive DCIS treated with BCS and radiation therapy and found no significant differences in local relapse, disease-free survival, or overall survival.[44] Although somewhat conflicting, these studies collectively suggest that the microinvasion in and of itself may not confer a worse prognosis; the clinical behavior may be related to the pathologic features of the underlying DCIS (eg, comedo necrosis, high-grade disease) (see Variant 5).

Pleomorphic Lobular Carcinoma in Situ

Pleomorphic lobular carcinoma in situ (PLCIS) is a histologic finding distinguished from classical lobular carcinoma in situ (LCIS) by enlarged and often irregular nuclei. PLCIS has features that are similar to those of high-grade DCIS—eg, comedo necrosis and microcalcifications—which can be detected radiographically in most cases. Biologically, PLCIS carries the hallmarks of a more aggressive entity than classical LCIS, including a high Ki-67 index, p53 protein accumulation, a lack of ER and progesterone receptor expression, and a tendency toward HER2 overexpression and amplification. Like classical LCIS, however, these lesions typically do not express E-cadherin and are therefore distinguishable from DCIS.[51]

The more aggressive histologic profile of PLCIS has led to recommendations for treatment as a precursor lesion to invasive malignancy (similar to DCIS), including resection to clear margins and consideration for adjuvant radiotherapy.[52-54] PLCIS has a higher rate of association with invasive malignancy than classical LCIS, strengthening the argument for complete excision.[55] At the time of this article’s publication, however, limited clinical data exist to support the malignant potential of PLCIS.[51] Thus, there is a paucity of evidence to support the routine use of radiotherapy in this setting (see Variant 6).

Use of Magnetic Resonance Imaging in DCIS

The use of breast magnetic resonance imaging (MRI) is increasingly prevalent in the preoperative
management of invasive breast cancers and, more recently, of DCIS. Early in the era of breast MRI, this mode of imaging was felt to be less sensitive than mammography for pure intraductal cancers[56]; thus, its use in the workup of DCIS was discouraged. More recently, it has become apparent that the diagnostic criteria for MRI assessment of DCIS differ from those of invasive cancers[57] and that MRI does allow for more effective diagnosis of DCIS.[58-60] Several studies indicate that breast MRI is more sensitive than mammography for detecting multicentric disease in DCIS.[59,60] For estimating the size of DCIS lesions using MRI, conflicting results have been published.[60-62] It is generally believed that MRI provides an overall improvement in size estimation for DCIS compared with mammography, but results in both overestimation and underestimation of tumor size compared with pathologic analysis.

Breast MRI has been found to be more sensitive for detecting intermediate- and high-grade DCIS.[61,62] Lastly, recent reports suggest that the varied morphology of DCIS seen on breast MRI is a reflection of the heterogeneous differences in DCIS pathology.[63] For example, clumped enhancement patterns are more often associated with high-grade lesions than are more heterogeneous patterns, and small focal masses are associated with ER-positive DCIS.

There are several advantages to using MRI in the preoperative setting: its high sensitivity for DCIS, ranging from 72% to 84%[64]; the possibility of detecting DCIS lesions without microcalcifications that are mammography-occult; its ability to better assess for multicentricity than mammography; its ability to outperform mammography in dense breasts; and its ability to improve on the size estimation for guiding local treatment decisions. These pluses have to be weighed against the disadvantages, which include high false-positive rates that would potentially require unnecessary further workup and additional invasive procedures, delay of definitive treatment for the known malignancy, and increased anxiety for the patient. It is important to note that although no studies to date demonstrate an improvement in outcomes with the use of MRI for DCIS, it has been shown to decrease the need for re-excisions secondary to incomplete surgical removal and positive margins.[61]

**Accelerated Partial-Breast Irradiation**

Although accelerated PBI is being increasingly used for breast cancer, there are no prospective randomized studies published to date reporting its long-term efficacy compared with standard conventionally fractionated whole-breast radiation. Although some well-controlled, prospective, single-arm studies exist for invasive cancers and for DCIS specifically, there is a paucity of such data. Although not a traditionally “prospective” study, the most notable experience of accelerated PBI for DCIS comes from the American Society of Breast Surgeons MammoSite® Registry Trial, an analysis of patient data collected from 97 institutions that allowed treating physicians to enter patient information at any time before, during, or after MammoSite® treatment, for future analysis and study. In the most recent update, of the 194 patients in the registry who had DCIS (13%), the 5-year actuarial local relapse was 3.39% with the use of MammoSite®, comparable to the rate in historic controls who received conventionally fractionated whole-breast radiation.[65]

A recently published subset analysis of the MammoSite® Registry Trial compared the outcomes of patients who would have met entry criteria for the E5194 trial with the ECOG trial results. Compared with historically matched control patients treated with excision alone in the E5194 trial, the MammoSite® patients had fewer recurrences at 5 years in both the low/intermediate-grade (0% vs 6.1%) and high-grade cohorts (5.3% vs 15.3%).[66] An independent prospective, multicenter trial, conducted between 2003 and 2009, of BCS plus MammoSite®, treated 41 DCIS patients (42 breasts). The 5-year actuarial rate of ipsilateral breast tumor recurrence was 11.3%; none of those recurrences were within the treatment area.[67]

Due to the limited data on use of the various accelerated PBI modalities for DCIS, the American Society for Radiation Oncology (ASTRO) recently published a consensus statement regarding the use of accelerated PBI, in which three categories of appropriateness were generated based on the level of prospective data and follow-up: suitable, cautionary, and unsuitable[68]; DCIS was categorized in the “cautionary” group. Similarly, the Breast Cancer Working Group of the Groupe Européen de Curiethérapie–European Society for Therapeutic Radiology and Oncology recently published guidelines that defined three categories for patient selection for accelerated PBI[69]; of these, DCIS was placed in the “intermediate-risk” group.

**Summary**

- Breast conservation therapy (consisting of breast-conserving surgery to achieve negative
margins, followed by adjuvant radiation therapy to the whole breast) is an acceptable treatment alternative to mastectomy for women with localized ductal carcinoma in situ (DCIS) wishing to conserve their breast.

- In selected older patients with fully excised, low-grade disease, observation may be considered after conservative surgery.
- When a mastectomy is desired or required, most surgeons will simultaneously perform a sentinel lymph node biopsy.
- Conventionally fractionated whole-breast radiation for DCIS consists of 45–50.4 Gy in 25–28 fractions, with or without a boost to the tumor bed.
- Although there are currently no phase III data to support the use of a boost in DCIS, most radiation oncologists will deliver a boost dose of 10–16 Gy, depending on patient age and margin status.
- Partial breast irradiation may be used in appropriately selected patients but should be delivered on protocol.
- Tamoxifen should be considered in estrogen receptor–positive patients with DCIS.
- DCIS with microinvasion is managed similarly to DCIS, except that SLNB is often used and regional nodal radiation therapy may be considered in selected cases.
- Hypofractionated whole-breast radiation for DCIS is being investigated in ongoing phase III studies, but it may be considered in appropriately selected patients.
- The use of MRI for DCIS remains unclear but may be considered in selected patients for whom there are concerns regarding additional disease that would alter the planned management.

A randomized phase III trial (of DCIS or invasive tumors ≤ 3 cm), recently closed to accrual, was designed to determine the relative efficacy and toxicity of accelerated PBI compared with whole-breast radiotherapy (NSABP B-39/RTOG 0413 trial).[70] Patients randomized to PBI received either luminal-based brachytherapy, interstitial brachytherapy, or 3D conformal external beam radiation therapy. Five-year data have been presented indicating low rates of high-grade toxicity with 3D conformal external beam accelerated PBI at a mean follow-up of 41 months (3% grade 3 toxicity; 0% grade 4-5). [71] Data are maturing to assess the overall efficacy of PBI, as well as of cosmesis and the brachytherapy toxicity profile (see Variant 7 and Variant 8).

**Hypofractionated Whole-Breast Radiation**

There has been a recent resurgence in the use of hypofractionated whole-breast radiation for women with early-stage breast cancer. Several single- and multi-institution series have demonstrated acceptable local failure rates with up to 5 years of follow-up for DCIS treated with accelerated whole-breast regimens.[72-74] There are now four prospective randomized trials confirming that treatment with accelerated hypofractionated radiation with doses of 39–43 Gy in 13-16 fractions provides local tumor control comparable to that provided by standard fractionation of 50 Gy in 25 fractions, with equivalent acute and late effects of treatment in patients with early-stage invasive breast cancers. Although these trials did not specifically assess hypofractionated radiation in DCIS patients, long-term data suggest no difference between hypofractionated whole-breast radiation and the standard fractionation in terms of local control, cosmesis, and other long-term effects in the setting of breast conservation. Although patients in these trials had invasive disease, the cosmetic and long-term effects would not be expected to be different in DCIS. While the presumption is that local control rates for DCIS using hypofractionated whole-breast radiation would be comparable to the standard fractionation schemes, patients with DCIS were excluded from the randomized hypofractionation whole-breast trials. However, many institutions have adopted use of hypofractionated regimens for DCIS, given the compelling results of retrospective series and reasonable parallels drawn to prospective data for early-stage invasive disease.

Based on the lack of available prospective randomized data, a recent ASTRO task force concluded that at this time there are insufficient data to allow an evidence-based recommendation for or against hypofractionated whole-breast radiation for women with DCIS.[75] The panel did feel that hypofractionation was equivalent to standard fractionation for T1-2 N0 tumors. Outside of tumor stage, selection criteria were age (≥ 50 years), dose heterogeneity (no more than ±7% along the central axis), and lack of systemic therapy. An ongoing randomized phase III study, the TROG 07.01/Breast International Group (BIG) 03-07/International Breast Cancer Study Group (IBCSG) 38-10 trial,[12] is studying radiation doses and fractionations specifically for DCIS of the breast. The RTOG
1005 trial[10] is also actively enrolling patients to investigate the utility of an integrated concurrent tumor bed boost within a 3-week hypofractionated whole-breast regimen. This phase III randomized comparison involves a control arm of whole-breast irradiation (with either conventional fractionation or hypofractionation) followed by a sequential boost in early-stage breast cancer (including DCIS) (see Variant 1, Variant 3, Variant 4, and Variant 5).

Postexcision Mammography

The use of the postexcision, preradiotherapy mammogram has previously been endorsed in a joint guideline by multiple national organizations to ensure removal of all suspicious-appearing microcalcifications.[76] It has been suggested that stereotactic localization and specimen radiography may not be enough to ensure removal of all such DCIS-associated microcalcifications, given the discontinuous growth pattern along duct lumens. Clinical data are lacking, however, to support a meaningful increase in local recurrence without the use of this imaging study. A recent large, single-institution review indicated that a postexcision mammogram would have prompted removal of residual DCIS in only 4% of patients (who would not have been re-excised regardless, for margin issues), a number in keeping with other published series.[77] The use of the postexcision mammogram was not associated with an improvement in 10-year local recurrence–free survival (94.8% vs 91.5%; \( P = .368 \)). Although there may not be compelling evidence for routine use of postexcision mammography, it can be an essential tool in cases of questionable margins or where specimen radiography is not done.

Management Guidelines

DCIS

Patients with DCIS are eligible for breast conservation when the area of involvement is amenable to complete surgical excision without compromise of ultimate cosmetic outcome. In general, this is defined as tumors ≤ 4–5 cm but requires consideration of tumor size and location relative to breast size, as well as patient preference for breast conservation, with joint input from the surgeon and radiation oncologist. Patients with extensive microcalcifications, large tumor size relative to small breast size, involvement of more than one quadrant, or multicentric disease should be considered for mastectomy. When undergoing mastectomy, an SLNB is a reasonable staging intervention. There is no consensus on the definition of negative margins. In general, trials using lumpectomy alone have required greater negative margin clearance (generally ≥ 3–10 mm) than those using definitive breast irradiation (ranging from no tumor on ink to 1–3 mm). It is clear that there is a correlation between the degree of margin clearance and local control.

Breast irradiation requires treatment to the whole breast with a total dose of 45–50.4 Gy in standard fractionation (1.8–2.0 Gy/day), with the option for a tumor bed boost to ensure that the total dose ranges between 50 Gy and 66 Gy, depending on pathologic findings. It remains unclear which patients are appropriate candidates for excision alone, but early results of observation in selected DCIS patients are promising.[27] The addition of tamoxifen in a hormone receptor–positive DCIS patient should be considered and weighed against the side effects of the medication.

At the time of this article’s publication, there are four phase III trials open to accrual pertaining to radiotherapy in the management of DCIS: RTOG 1005,[10] which is comparing a hypofractionated concomitant boost whole-breast regimen with a sequential boost approach in early-stage breast cancer; NSABP B-43,[11] which is assessing the use of adjuvant trastuzumab in HER2-positive DCIS patients; TROG 07.01/BIG 03-07/ICSG 38-10,[12] which is studying radiation doses and fractionation in DCIS; and BONBIS,[13] which is studying the utility of tumor bed boost with whole-breast irradiation in DCIS.

DCIS with microinvasion

Eligibility for breast conservation in patients with DCIS and microinvasion requires the same clinical and pathologic considerations as those for DCIS patients with regard to tumor size, tumor location, breast size, and the feasibility of complete excision. This scenario differs, however, in the distinctly increased but low possibility of axillary node involvement and occult systemic metastatic disease. If knowledge of positive axillary nodes would prompt a recommendation for systemic therapy, an SLNB (by a surgeon experienced in this technique) may be performed or irradiation of the axilla may be done, depending on the clinical situation.
Breast irradiation involves treatment to the whole breast with a total dose of 45–50.4 Gy in standard fractionation, with the option for a tumor bed boost to ensure that the total dose ranges between 50 Gy and 66 Gy, depending on pathologic findings. Treatment with lumpectomy and tamoxifen without breast radiotherapy in elderly women with ER-positive microinvasive tumors may be considered. Tamoxifen should be considered for hormone receptor–positive patients. Aromatase inhibitors are also an option for postmenopausal patients in whom anti-endocrine therapy is being considered. The results of two phase III studies comparing their use to that of tamoxifen for adjuvant management of DCIS are currently being analyzed (IBIS-II DCIS and NSABP B-35 trials).

The American College of Radiology seeks and encourages collaboration with other organizations on the development of the ACR Appropriateness Criteria through society representation on expert panels. Participation by representatives from collaborating societies on the expert panel does not necessarily imply individual or society endorsement of the final document.

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Variant 1: A 55-year-old woman with mammographically detected, 2-cm, c...

Variant 2: A 50-year-old woman with extensive pleomorphic microcalcifi...
**Variant 3:** A 78-year-old woman with mammographically detected, 1-cm, I...

**Variant 4:** A 41-year-old premenopausal woman with mammographically det...

**Variant 6:** A 60-year-old woman with new microcalcifications on screeni...

**Variant 5:** A 49-year-old premenopausal woman with mammographically det...
Variant 7: A 41-year-old premenopausal woman with mammographically det... Variant 8 A 58-year-old postmenopausal woman with mammographically det...

References:


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