Date of origin: 1996
Last review date: 2014

American College of Radiology
ACR Appropriateness Criteria®

DUCTAL CARCINOMA IN SITU

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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 improved screening utilization and imaging techniques. This has led to a shift in disease presentation from years past where 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 myoepithilial 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 2 architectural subtypes. Although pathologic criteria have been established to classify DCIS in comparison to 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 particularly be difficult, as demonstrated by significant differences in diagnosis on expert pathology review [3,4].

There are 3 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 5–7 weeks. In more recent years, there has been a resurgence of 2 accelerated regimens for both DCIS and invasive breast cancers: 1) accelerated partial-breast irradiation (PBI), delivering 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 to mastectomy for DCIS, comparisons of BCT to historic mastectomy controls suggest no difference in overall survival. In terms of breast conservation, there are 4 published randomized trials for DCIS

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evaluating the benefit of adjuvant whole-breast radiotherapy after local excision: the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-17 [5,6], the European Organization for Research and Treatment of Cancer (EORTC) 10853 [7], the UK/Australia/New Zealand (UK/ANZ) cooperative trial [8], and the Swedish trial [9]. All suggest 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 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. Furthermore, the randomized data assess the benefit of adjuvant, whole-breast radiation after local excision, but a more recent trend toward PBI has not been adequately studied. The existing body of 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 of patients have subclinical disease at presentation that is subsequently detected, mainly by mammography. Furthermore, 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 also 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 document is on local treatment management and prevention of local relapse, tamoxifen and other antiendocrine 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: Radiation Therapy Oncology Group® (RTOG®) 1005 [10], NSABP B-43 [11], Tasman Radiation Oncology Group (TROG) 07.01 [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%–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 outcome after treatment with mastectomy shows survival rates of 96%–100%. Local-regional control rates are also reported as 96%–100% [14,15]. 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%–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 2 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 (where patients may elect 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 3 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. Can be divided into 3 delivery methods:
   - Standard, conventionally fractionated, whole-breast radiation (delivered daily over 5 weeks with or without boost)
   - Accelerated PBI, where 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 both the addition of radiotherapy and tamoxifen have been shown to independently improve local control in randomized, prospective studies, the question remains whether subsets of DCIS patients have limited benefit and can forego 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 demonstrate breast failure rates of 16%–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 NSABP B-06 (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 versus excision followed by radiation therapy were 43% and 7%, respectively, at a mean follow-up interval of 83 months [14].

As mentioned above, 4 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, NSABP B-17, has the longest follow-up of 20 years. It randomized patients after lumpectomy to radiation versus 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 has a greater impact on reducing the incidence of invasive recurrences, the potentially life-threatening form of recurrence (relative risk [RR] = 0.38, P=0.00001) but also significantly reduces noninvasive recurrences (RR = 0.49, P=0.001). 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 for DCIS randomized patients after lumpectomy to radiation versus no radiation without 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 additional of breast radiation (P<0.001). 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 versus 2.0% per year with the addition of radiotherapy. These rates decreased to 2.0% and 1.2% in the second 5 years, and 1.3% and 0.6% after that.

Similar to the long-term outcomes in the B-17 trial, radiation significantly reduced invasive and DCIS recurrences in this trial. Factors that predicted an increased local recurrence on multivariate analysis included age 40 years or younger, 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 2x2 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% versus 7.1%, P<0.0001).

A phase III trial originating from Sweden (the SweDCIS Trial) [9] also demonstrated a benefit to 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% CI, 0.30 to 0.54). A notable difference in this protocol from 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 4 trials were pooled in a meta-analysis performed by the Early Breast Cancer Trialists' Collaborative Group [21]. The 10-year risk reduction of any ipsilateral breast event was 15.2% (12.9% versus 28.1%, P<0.00001); effectiveness was significant regardless of risk factors such as age, grade, margin status, detection method, tumor size, presence of comedonecrosis, or use of tamoxifen. As with the individual trials, no difference in overall survival was observed.

The results of the RTOG 98-04 were recently presented at 2 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 ≤2.5 cm, and margins ≥3 mm). Although the trial closed early due to low accrual, the 7-year recurrence rates were 6.7% without radiotherapy versus 0.9% with (P=0.0003), corresponding to a hazard ratio of 0.11. Of note, though the majority was treated with standard fractionation, 8.4% of the patients 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 5 of these randomized, prospective trials have consistently demonstrated a significant improvement in local control with the use of adjuvant radiation, with a risk reduction of both invasive and in-situ ipsilateral breast recurrence rates of >50% with the addition of postlumpectomy whole-breast radiotherapy, 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 that may be 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; with local failure rates reported to be 10%–15%, comparable to single-institution reports of surgical excision followed by radiation therapy in less rigorously selected patients. These series also note 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 from 2 institutions [25], continues to be used by some practitioners as part of their decision-making process for adjuvant radiation after local excision. It is important to note that the data from this "scoring system" were derived from retrospective data and that all randomized prospective 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 notable single-arm prospective protocol of highly selected small, low-grade DCIS patients 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 RTOG 98-04 trial discussed previously, which was designed to assess the outcomes of observed versus 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 stratification of the 2 cohorts in this study included the low-risk group, defined as low-grade or intermediate-grade DCIS measuring ≤2.5 cm; and the intermediate-risk group, defined as high-grade DCIS measuring ≤1 cm 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. 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 this increased to 10.5% and 18.0%. Given the long natural history of DCIS, often with late recurrences (>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 2 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 to excision alone on E5194 for both the low-risk (1.5% versus 6.1%) and high-risk groups (2% versus 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 those for whom radiotherapy would be of minimal benefit. Further validation is necessary before routine use of this genetic profile in determining clinical decisions [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 antiendocrine therapy to treat organs beyond the breast). However, BCT has been improved (yet made more complex) by the recent appreciation that antiendocrine 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% confidence interval [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 with patients with estrogen-receptor (ER)-positive only. 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 on B-17 and 163 months on 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 on 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 IBIS-II/BIG 5-02 (http://www.ibis-trials.org/thetrials/ibistrials/ibis-2-dcis) have completed accrual in the comparison of anastrazole to 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 trastuzamab for HER2/neu-positive DCIS is being evaluated in a phase III trial of adjuvant trastuzamab in the NSABP B-43 trial [11], in which patients will receive 6 weeks of whole-breast irradiation and be randomized to 2 cycles of trastuzamab delivered concurrently with radiation versus 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 preinvasive 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%–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) versus pure DCIS after definitive surgery (5% node positive) [35,36] as well as DCIS with microinvasion (9% node positive) versus 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 the definitive local surgery.

From the more detailed histopathologic evaluation of lymph nodes removed from SLNB compared to 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 institutional 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 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 considered as having "minimal invasion" but should be distinguished from microinvasion (T1mic) as an invasive cancer (T1a).

Limited information has been reported regarding treatment outcome 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 than 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 node dissection and the large impact a positive lymph node would potentially have on systemic management of a patient with a microinvasive primary. Many clinicians now include pathologic axillary staging (for example, 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 pure DCIS is that lumpectomy alone is not considered a standard management 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 will be receiving adjuvant hormonal therapy. In the Cancer and Leukemia Group B (CALGB) randomized trial of lumpectomy followed by tamoxifen alone versus tamoxifen and radiation for women 70 years of age and older 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% versus 91% at 10 years) [48]. Although the existing data on DCIS with microinvasion are retrospective with small numbers of patients [47,49,50], a recent relatively large, single institutional series reported long-term outcomes of pure DCIS compared to microinvasive DCIS treated with BCS and radiation therapy and found no significant differences in local relapse, disease-free survival, or overall survival [44]. Though 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 similar to high-grade DCIS such as comedonecrosis 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 estrogen 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 writing, however, limited clinical data exist to support the malignant potential for PLCIS [51]. As such, there is a paucity of evidence to support the routine use of radiotherapy (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, for 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 in detecting multicentric disease for DCIS compared with mammography [59,60]. For estimating the size of DCIS lesions using MRI, conflicting results have been published [60-62]. Generally it is felt that MRI provides an overall improvement of size estimation for DCIS

compared with mammography but with 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 of DCIS pathology [63]. For example, clumped enhancement patterns are more associated with high-grade lesions than more heterogeneous patterns, and small focal masses are associated with ER-positive DCIS. There are several advantages in using an MRI in the preoperative setting: its high sensitivity for DCIS that ranges from 72% to 84% [64]; the possibility of detecting DCIS 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, including high false-positive rates potentially requiring 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 a benefit in outcomes with the use of MRI for DCIS, the use of breast MRI in DCIS has been shown to decrease the need for re-excisions secondary to incomplete surgical removal and positive margins [61].

Accelerated Partial Breast Radiation

Though accelerated PBI is being increasingly used for breast cancer, there are no randomized, prospective 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. Though 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 for 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, at 5 years, of the 194 (13%) patients in the registry who had DCIS, the 5-year actuarial local relapse was 3.39% with the use of Mammosite®, comparable to historic controls of conventionally fractionated, whole-breast radiation [65]. A recently published subset analysis of the Mammosite® registry trial compared the outcomes of those patients who would have met entry criteria for the E5194 trial with the ECOG trial results. Compared to historically matched control patients treated with excision alone on the E5194 trial, the Mammosite® patients had fewer recurrences at 5 years for both the low/intermediate grade (0% versus 6.1%) and the high-grade cohorts (5.3% versus 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 IBTR was 11.3%; none of those recurrences were within the treatment area [67].

Due to the limited data using the various accelerated PBI modalities for DCIS, the American Society for Radiology Oncology (ASTRO) recently published a consensus statement regarding the use of accelerated PBI, where 3 categories of appropriateness were generated based on the level of prospective data and follow-up: suitable, cautionary, and unsuitable [68]. Due to the limited prospective data on PBI for DCIS, this disease entity was categorized in the "cautionary" group. Similarly, the Breast Cancer Working Group of the Groupe European de Curietherapie and the European Society of Therapeutic Radiology recently published guidelines of 3 categories for patient selection for accelerated PBI [69] where DCIS was placed in the "intermediate" risk group.

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

Hypofractionated Whole-Breast Radiation

There has been a recent resurgence 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 4 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 in hypofractionated, whole-breast radiation compared to 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. Though 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 with 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 hypofractionation was equivalent to standard fractionation for T1-2 N0 tumors. Outside of tumor stage, selection criteria were age (50 or greater), dose heterogeneity (no more than +/-7% along the central axis), and lack of systemic therapy. An ongoing, randomized phase III study, TROG 07.01/BIG 03-07/IBCSG Trial 38-10 [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 a postexcision mammogram would have prompted removal of residual DCIS in only 4% of cases (that 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% versus 91.5%, P=0.368). Though 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 and 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 to 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 writing, there are 4 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 herceptin in HER2+ DCIS patients, TROG 07.01/BIG 03-07/IBCSG 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, a 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 to 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 following lumpectomy and negative margins may be considered.

Tamoxifen should be considered for hormone-receptor-positive patients. Aromatase inhibitors are also an option for postmenopausal patients in whom antiendocrine therapy is being considered, and the results of 2 phase III studies comparing their use to that of tamoxifen for adjuvant management of DCIS are currently being analyzed (IBIS II DCIS/BIG 5-02 and NSABP B-35).

Summary of Recommendations

- BCT therapy (consists of BCS to achieve negative margins followed by adjuvant radiation therapy to the whole breast) is an acceptable treatment alternative to mastectomy for women with localized 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 SLNB.
- 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.
- Though 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 age and margin status.
- PBI may be used in appropriately selected patients but should be delivered on protocol.
- Tamoxifen should be considered in ER-positive patients with DCIS.
- DCIS with microinvasion is managed similarly to DCIS, except that SLNB is often used and regional nodal RT 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.

Summary of Evidence

Of the 77 references cited in the *ACR Appropriateness Criteria® Ductal Carcinoma in Situ* document, 59 are categorized as therapeutic references including 10 well-designed studies, and 21 good quality studies. Additionally, 18 references are categorized as diagnostic references including 2 good quality studies, and 8 quality studies that may have design limitations. There are 36 references that may not be useful as primary evidence.

The 77 references cited in the *ACR Appropriateness Criteria® Ductal Carcinoma in Situ* document were published between 1991-2013.

While there are references that report on studies with design limitations, 33 well-designed or good quality studies provide good evidence.

Supporting Documents

For additional information on the Appropriateness Criteria methodology and other supporting documents go to www.acr.org/ac.

References

1. Consensus Conference on the classification of ductal carcinoma in situ. The Consensus Conference Committee. *Cancer.* 1997;80(9):1798-1802.
2. Lester SC, Bose S, Chen YY, et al. Protocol for the examination of specimens from patients with ductal carcinoma in situ of the breast. *Arch Pathol Lab Med.* 2009;133(1):15-25.
3. Rosai J. Borderline epithelial lesions of the breast. *Am J Surg Pathol.* 1991;15(3):209-221.
4. Sloane JP, Ellman R, Anderson TJ, et al. Consistency of histopathological reporting of breast lesions detected by screening: findings of the U.K. National External Quality Assessment (EQA) Scheme. U. K. National Coordinating Group for Breast Screening Pathology. *Eur J Cancer.* 1994;30A(10):1414-1419.
5. Fisher B, Dignam J, Wolmark N, et al. Lumpectomy and radiation therapy for the treatment of intraductal breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-17. *J Clin Oncol.* 1998;16(2):441-452.
6. Fisher ER, Costantino J, Fisher B, Palekar AS, Redmond C, Mamounas E. Pathologic findings from the National Surgical Adjuvant Breast Project (NSABP) Protocol B-17. Intraductal carcinoma (ductal carcinoma in situ). The National Surgical Adjuvant Breast and Bowel Project Collaborating Investigators. *Cancer.* 1995;75(6):1310-1319.
7. Donker M, Litiere S, Werutsky G, et al. Breast-conserving treatment with or without radiotherapy in ductal carcinoma In Situ: 15-year recurrence rates and outcome after a recurrence, from the EORTC 10853 randomized phase III trial. *J Clin Oncol.* 2013;31(32):4054-4059.
8. Cuzick J, Sestak I, Pinder SE, et al. Effect of tamoxifen and radiotherapy in women with locally excised ductal carcinoma in situ: long-term results from the UK/ANZ DCIS trial. *Lancet Oncol.* 2011;12(1):21-29.
9. Holmberg L, Garmo H, Granstrand B, et al. Absolute risk reductions for local recurrence after postoperative radiotherapy after sector resection for ductal carcinoma in situ of the breast. *J Clin Oncol.* 2008;26(8):1247-1252.
10. National Cancer Institute (NCI). A Phase III Trial of Accelerated Whole Breast Irradiation With Hypofractionation Plus Concurrent Boost Versus Standard Whole Breast Irradiation Plus Sequential Boost for Early-Stage Breast Cancer. In: ClinicalTrials.gov. Bethesda (MD): National Library of Medicine (US). October 29, 2013. Available from: http://clinicaltrials.gov/ct2/show/NCT01349322?term=NCT01349322. NLM Identifier: NCT01349322.
11. National Cancer Institute (NCI). A Phase III Clinical Trial Comparing Trastuzumab Given Concurrently With Radiation Therapy and Radiation Therapy Alone for Women With HER2-Positive Ductal Carcinoma In Situ Resected by Lumpectomy. In: ClinicalTrials.gov. Bethesda (MD): National Library of Medicine (US). October 29, 2013. Available from: http://clinicaltrials.gov/ct2/show/study/NCT00769379. NLM Identifier: NCT00769379.
12. National Cancer Institute (NCI). A Randomised Phase III Study of Radiation Doses and Fractionation Schedules in Non-low Risk Ductal Carcinoma In Situ (DCIS) of the Breast. In: ClinicalTrials.gov. Bethesda (MD): National Library of Medicine (US). October 29, 2013. Available from: http://clinicaltrials.gov/ct2/show/NCT00470236?term=NCT00470236. NLM Identifier: NCT00470236.
13. National Cancer Institute (NCI). A Multicentric Phase III Trial Evaluating the Impact of a Radiation Boost (16Gy) After Breast Conserving Surgery and a Whole Breast Irradiation (50Gy) for DCIS. In: ClinicalTrials.gov. Bethesda (MD): National Library of Medicine (US). October 29, 2013. Available from: http://clinicaltrials.gov/ct2/show/NCT00907868?term=NCT00907868. NLM Identifier: NCT00907868.
14. Fisher ER, Leeming R, Anderson S, Redmond C, Fisher B. Conservative management of intraductal carcinoma (DCIS) of the breast. Collaborating NSABP investigators. *J Surg Oncol.* 1991;47(3):139-147.
15. O'Sullivan MJ, Morrow M. Ductal carcinoma in situ--current management. *Surg Clin North Am.* 2007;87(2):333-351, viii.
16. American College of Radiology. ACR Appropriateness Criteria®: Postmastectomy Radiotherapy. Available at: http://www.acr.org/~/media/ACR/Documents/AppCriteria/Oncology/PostmastectomyRadiotherapy.pdf. Accessed December 10, 2013.

17. Shaitelman SF, Wilkinson JB, Kestin LL, et al. Long-term outcome in patients with ductal carcinoma in situ treated with breast-conserving therapy: implications for optimal follow-up strategies. *Int J Radiat Oncol Biol Phys.* 2012;83(3):e305-312.
18. Wilkinson JB, Vicini FA, Shah C, et al. Twenty-year outcomes after breast-conserving surgery and definitive radiotherapy for mammographically detected ductal carcinoma in situ. *Ann Surg Oncol.* 2012;19(12):3785-3791.
19. Solin LJ, Fourquet A, Vicini FA, et al. Long-term outcome after breast-conservation treatment with radiation for mammographically detected ductal carcinoma in situ of the breast. *Cancer.* 2005;103(6):1137-1146.
20. Wapnir IL, Dignam JJ, Fisher B, et al. Long-term outcomes of invasive ipsilateral breast tumor recurrences after lumpectomy in NSABP B-17 and B-24 randomized clinical trials for DCIS. *J Natl Cancer Inst.* 2011;103(6):478-488.
21. Correa C, McGale P, Taylor C, et al. Overview of the randomized trials of radiotherapy in ductal carcinoma in situ of the breast. *J Natl Cancer Inst Monogr.* 2010;2010(41):162-177.
22. McCormick B, Moughan J, Hudis C, et al. Low-risk Breast Ductal Carcinoma In Situ (DCIS): Results From the Radiation Therapy Oncology Group 9804 Phase 3 Trial. *International journal of radiation oncology, biology, physics.* 2012;84(3):S5.
23. McCormick B. RTOG 9804: A prospective randomized trial for "good risk" ductal carcinoma in situ (DCIS), comparing radiation (RT) to observation (OBS). *J Clin Oncol.* 2012;30:(suppl; abstr 1004).
24. Silverstein MJ, Lagios MD, Groshen S, et al. The influence of margin width on local control of ductal carcinoma in situ of the breast. *N Engl J Med.* 1999;340(19):1455-1461.
25. Silverstein MJ, Lagios MD. Choosing treatment for patients with ductal carcinoma in situ: fine tuning the University of Southern California/Van Nuys Prognostic Index. *J Natl Cancer Inst Monogr.* 2010;2010(41):193-196.
26. Wong JS, Kaelin CM, Troyan SL, et al. Prospective study of wide excision alone for ductal carcinoma in situ of the breast. *J Clin Oncol.* 2006;24(7):1031-1036.
27. Hughes LL, Wang M, Page DL, et al. Local excision alone without irradiation for ductal carcinoma in situ of the breast: a trial of the Eastern Cooperative Oncology Group. *J Clin Oncol.* 2009;27(32):5319-5324.
28. Motwani SB, Goyal S, Moran MS, Chhabra A, Haffty BG. Ductal carcinoma in situ treated with breast-conserving surgery and radiotherapy: a comparison with ECOG study 5194. *Cancer.* 2011;117(6):1156-1162.
29. Solin LJ, Gray R, Baehner FL, et al. A multigene expression assay to predict local recurrence risk for ductal carcinoma in situ of the breast. *J Natl Cancer Inst.* 2013;105(10):701-710.
30. Fisher B, Dignam J, Wolmark N, et al. Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial. *Lancet.* 1999;353(9169):1993-2000.
31. Allred DC, Anderson SJ, Paik S, et al. Adjuvant tamoxifen reduces subsequent breast cancer in women with estrogen receptor-positive ductal carcinoma in situ: a study based on NSABP protocol B-24. *J Clin Oncol.* 2012;30(12):1268-1273.
32. Allred DC, Clark GM, Molina R, et al. Overexpression of HER-2/neu and its relationship with other prognostic factors change during the progression of in situ to invasive breast cancer. *Hum Pathol.* 1992;23(9):974-979.
33. Bruening W, Fontanarosa J, Tipton K, Treadwell JR, Launders J, Schoelles K. Systematic review: comparative effectiveness of core-needle and open surgical biopsy to diagnose breast lesions. *Ann Intern Med.* 2010;152(4):238-246.
34. Moran CJ, Kell MR, Flanagan FL, Kennedy M, Gorey TF, Kerin MJ. Role of sentinel lymph node biopsy in high-risk ductal carcinoma in situ patients. *Am J Surg.* 2007;194(2):172-175.
35. Meijnen P, Oldenburg HS, Loo CE, Nieweg OE, Peterse JL, Rutgers EJ. Risk of invasion and axillary lymph node metastasis in ductal carcinoma in situ diagnosed by core-needle biopsy. *Br J Surg.* 2007;94(8):952-956.
36. Yi M, Krishnamurthy S, Kuerer HM, et al. Role of primary tumor characteristics in predicting positive sentinel lymph nodes in patients with ductal carcinoma in situ or microinvasive breast cancer. *Am J Surg.* 2008;196(1):81-87.
37. Katz A, Gage I, Evans S, et al. Sentinel lymph node positivity of patients with ductal carcinoma in situ or microinvasive breast cancer. *Am J Surg.* 2006;191(6):761-766.
38. Sakr R, Bezu C, Raoust I, et al. The sentinel lymph node procedure for patients with preoperative diagnosis of ductal carcinoma in situ: risk factors for unsuspected invasive disease and for metastatic sentinel lymph nodes. *Int J Clin Pract.* 2008;62(11):1730-1735.

39. Farkas EA, Stolier AJ, Teng SC, Bolton JS, Fuhrman GM. An argument against routine sentinel node mapping for DCIS. *Am Surg.* 2004;70(1):13-17; discussion 17-18.
40. Intra M, Veronesi P, Mazzarol G, et al. Axillary sentinel lymph node biopsy in patients with pure ductal carcinoma in situ of the breast. *Arch Surg.* 2003;138(3):309-313.
41. Lara JF, Young SM, Velilla RE, Santoro EJ, Templeton SF. The relevance of occult axillary micrometastasis in ductal carcinoma in situ: a clinicopathologic study with long-term follow-up. *Cancer.* 2003;98(10):2105-2113.
42. Moore KH, Sweeney KJ, Wilson ME, et al. Outcomes for women with ductal carcinoma-in-situ and a positive sentinel node: a multi-institutional audit. *Ann Surg Oncol.* 2007;14(10):2911-2917.
43. Dominguez FJ, Golshan M, Black DM, et al. Sentinel node biopsy is important in mastectomy for ductal carcinoma in situ. *Ann Surg Oncol.* 2008;15(1):268-273.
44. Parikh RR, Haffty BG, Lannin D, Moran MS. Ductal carcinoma in situ with microinvasion: prognostic implications, long-term outcomes, and role of axillary evaluation. *Int J Radiat Oncol Biol Phys.* 2012;82(1):7-13.
45. Solin LJ, Fowble BL, Yeh IT, et al. Microinvasive ductal carcinoma of the breast treated with breast-conserving surgery and definitive irradiation. *Int J Radiat Oncol Biol Phys.* 1992;23(5):961-968.
46. Sue GR, Lannin DR, Killelea B, Chagpar AB. Predictors of microinvasion and its prognostic role in ductal carcinoma in situ. *Am J Surg.* 2013;206(4):478-481.
47. Vieira CC, Mercado CL, Cangiarella JF, Moy L, Toth HK, Guth AA. Microinvasive ductal carcinoma in situ: clinical presentation, imaging features, pathologic findings, and outcome. *Eur J Radiol.* 2010;73(1):102-107.
48. Hughes KS, Schnaper LA, Bellon JR, et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. *J Clin Oncol.* 2013;31(19):2382-2387.
49. Cavaliere A, Scheibel M, Bellezza G, et al. Ductal carcinoma in situ with microinvasion: clinicopathologic study and biopathologic profile. *Pathol Res Pract.* 2006;202(3):131-135.
50. Margalit DN, Sreedhara M, Chen YH, et al. Microinvasive breast cancer: ER, PR, and HER-2/neu status and clinical outcomes after breast-conserving therapy or mastectomy. *Ann Surg Oncol.* 2013;20(3):811-818.
51. Masannat YA, Bains SK, Pinder SE, Purushotham AD. Challenges in the management of pleomorphic lobular carcinoma in situ of the breast. *Breast.* 2013;22(2):194-196.
52. NCCN Clinical Practice Guidelines in Oncology. Breast Cancer. Version 3.2013. 2013; Available at: http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed October 20, 2013.
53. Ibarra JA. Pleomorphic Lobular Neoplasia of the Breast. ABSD Advisor 2013. 2013:3-8.
54. Laenkholm AV, Jensen MB, Kroman N, Rank F. Breast cancer in situ. From pre-malignant lesion of uncertain significance to well-defined non-invasive malignant lesion. The Danish Breast Cancer Cooperative Group Register 1977-2007 revisited. *Acta Oncol.* 2008;47(4):765-771.
55. Carder PJ, Shaaban A, Alizadeh Y, Kumarasuwamy V, Liston JC, Sharma N. Screen-detected pleomorphic lobular carcinoma in situ (PLCIS): risk of concurrent invasive malignancy following a core biopsy diagnosis. *Histopathology.* 2010;57(3):472-478.
56. Bazzocchi M, Zuiani C, Panizza P, et al. Contrast-enhanced breast MRI in patients with suspicious microcalcifications on mammography: results of a multicenter trial. *AJR Am J Roentgenol.* 2006;186(6):1723-1732.
57. Raza S, Vallejo M, Chikarmane SA, Birdwell RL. Pure ductal carcinoma in situ: a range of MRI features. *AJR Am J Roentgenol.* 2008;191(3):689-699.
58. Kuhl CK, Schrading S, Bieling HB, et al. MRI for diagnosis of pure ductal carcinoma in situ: a prospective observational study. *Lancet.* 2007;370(9586):485-492.
59. Menell JH, Morris EA, Dershaw DD, Abramson AF, Brogi E, Liberman L. Determination of the presence and extent of pure ductal carcinoma in situ by mammography and magnetic resonance imaging. *Breast J.* 2005;11(6):382-390.
60. Santamaria G, Velasco M, Farrus B, Zanon G, Fernandez PL. Preoperative MRI of pure intraductal breast carcinoma--a valuable adjunct to mammography in assessing cancer extent. *Breast.* 2008;17(2):186-194.
61. Schouten van der Velden AP, Boetes C, Bult P, Wobbes T. The value of magnetic resonance imaging in diagnosis and size assessment of in situ and small invasive breast carcinoma. *Am J Surg.* 2006;192(2):172-178.

62. Shiraishi A, Kurosaki Y, Maehara T, Suzuki M, Kurosumi M. Extension of ductal carcinoma in situ: histopathological association with MR imaging and mammography. *Magn Reson Med Sci.* 2003;2(4):159-163.
63. Esserman LJ, Kumar AS, Herrera AF, et al. Magnetic resonance imaging captures the biology of ductal carcinoma in situ. *J Clin Oncol.* 2006;24(28):4603-4610.
64. Estevez LG, Alvarez I, Segui MA, et al. Current perspectives of treatment of ductal carcinoma in situ. *Cancer Treat Rev.* 2010;36(7):507-517.
65. Jeruss JS, Kuerer HM, Beitsch PD, Vicini FA, Keisch M. Update on DCIS outcomes from the American Society of Breast Surgeons accelerated partial breast irradiation registry trial. *Ann Surg Oncol.* 2011;18(1):65-71.
66. Goyal S, Vicini F, Beitsch PD, et al. Ductal carcinoma in situ treated with breast-conserving surgery and accelerated partial breast irradiation: comparison of the Mammosite registry trial with intergroup study E5194. *Cancer.* 2011;117(6):1149-1155.
67. Abbott AM, Portschy PR, Lee C, et al. Prospective multicenter trial evaluating balloon-catheter partial-breast irradiation for ductal carcinoma in situ. *Int J Radiat Oncol Biol Phys.* 2013;87(3):494-498.
68. Smith BD, Arthur DW, Buchholz TA, et al. Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO). *Int J Radiat Oncol Biol Phys.* 2009;74(4):987-1001.
69. Polgar C, Van Limbergen E, Potter R, et al. Patient selection for accelerated partial-breast irradiation (APBI) after breast-conserving surgery: recommendations of the Groupe Europeen de Curietherapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) breast cancer working group based on clinical evidence (2009). *Radiother Oncol.* 2010;94(3):264-273.
70. RTOG 0413 Protocol Information. NSABP B-39: A Randomized Phase III Study of Conventional Whole Breast Irradiation (WBI) versus Partial Breast Irradiation (PBI) for Women with Stage 0, I, or II Breast Cancer. In: RTOG Radiation Therapy Oncology Group. Philadelphia (PA): October 29, 2013. Available from: http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0413.
71. Julian TB, Costantino JP, Vicini FA, et al. Early toxicity results with 3D conformal external beam therapy (CEBT) from the NSABP B-39/RTOG 0413 accelerated partial breast irradiation (APBI) trial. *ASCO Meeting Abstracts.* 2011;29(15_suppl):1011.
72. Ciervide R, Dhage S, Guth A, et al. Five year outcome of 145 patients with ductal carcinoma in situ (DCIS) after accelerated breast radiotherapy. *Int J Radiat Oncol Biol Phys.* 2012;83(2):e159-164.
73. Williamson D, Dinniwell R, Fung S, Pintilie M, Done SJ, Fyles AW. Local control with conventional and hypofractionated adjuvant radiotherapy after breast-conserving surgery for ductal carcinoma in-situ. *Radiother Oncol.* 2010;95(3):317-320.
74. Hathout L, Hijal T, Theberge V, et al. Hypofractionated radiation therapy for breast ductal carcinoma in situ. *Int J Radiat Oncol Biol Phys.* 2013;87(5):1058-1063.
75. Smith BD, Bentzen SM, Correa CR, et al. Fractionation for Whole Breast Irradiation: An American Society for Radiation Oncology (ASTRO) Evidence-Based Guideline. *Int J Radiat Oncol Biol Phys.* 2011;81(1):59-68.
76. Morrow M, Strom EA, Bassett LW, et al. Standard for the management of ductal carcinoma in situ of the breast (DCIS). *CA Cancer J Clin.* 2002;52(5):256-276.
77. Whaley JT, Lester-Coll NH, Morrissey SM, Milby AB, Hwang W-T, Prosnitz RG. Use of postexcision preirradiation mammography in patients with ductal carcinoma in situ of the breast treated with breast-conserving therapy. *Practical Radiation Oncology.* 2013;3(3):e107-e112.

Clinical Condition: **Ductal Carcinoma in Situ**

Variant 1: **55-year-old woman with mammographically detected 2.0-cm comedo, high nuclear grade DCIS, ER-positive. Surgically excised, multiple foci of DCIS in lateral and medial specimen close to excision margin (≤1.0 mm).**

Treatment	Rating	Comments
Principles of Treatment		
Re-excision lumpectomy and RT if margins negative	9	
Mastectomy with LN staging	8	
Mastectomy without LN staging	7	Most surgeons would perform a SLNB.
Breast MRI prior to additional surgery	4	
Re-excision lumpectomy alone, no RT	2	
RT alone, no re-excision	2	
RT Volumes (Assuming re-excision with widely negative margins)		
Whole breast	9	
Boost to tumor bed	8	
PBI (assuming re-excision with widely negative margins)	4	This treatment is awaiting maturation of clinical trial data. It should be considered on protocol. Cautionary subgroup based on age and DCIS.
RT Doses (1.8–2.0 Gy/day unless otherwise specified)		
Whole breast: 42.5 Gy/16 fractions	7	Consider this treatment without boost.
Whole breast: 45–46.8 Gy/23–26 fractions	8	Consider this treatment with or without boost.
Whole breast: 50–50.4 Gy/25–28 fractions	9	Consider this treatment with or without boost.
Total cumulative dose: 40 Gy	3	
Boost dose 10 Gy in 2 Gy fractions after WBRT dose of 50 Gy (assume <1 mm margins, no re-excision)	3	A higher boost is indicated for close surgical margins.
Boost dose 16 Gy in 2 Gy fractions after WBRT dose of 50 Gy (assume <1 mm margins, no re-excision)	7	Though there are no phase III data for DCIS, most radiation oncologists would include a boost dose.
Boost dose 10 Gy in 2 Gy fractions (assume re-excision, widely negative margin of >1.0 cm)	7	Though there are no phase III data for DCIS, most radiation oncologists would include a boost dose.
Boost dose 16 Gy in 2 Gy fractions (assume re-excision, widely negative margin of >1.0 cm)	6	A boost dose of 16 Gy may be higher than necessary with widely negative margins.
Systemic Therapy		
Tamoxifen (5 years) after lumpectomy + RT	8	

Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**

Clinical Condition: **Ductal Carcinoma in Situ**

Variant 2: **50-year-old woman with extensive pleomorphic microcalcifications in more than one quadrant on mammography. Area too large to excise with cosmetically acceptable outcome. Core biopsies demonstrate DCIS involving more than one quadrant.**

Treatment	Rating	Comments
Principles of Treatment		
Mastectomy with SLNB	9	
Mastectomy without LN staging	4	Most surgeons would perform a SLNB with mastectomy.
Mastectomy with ALND	2	A full level I/II axillary dissection is not indicated without evidence of involved lymph nodes.
Attempt at lumpectomy with adjuvant RT	2	Consider this treatment in the case of microcalcifications in more than one quadrant.
Attempt at lumpectomy, LN staging, adjuvant RT	2	
Breast MRI prior to definitive surgery	2	This treatment provides no additional information if microcalcifications and biopsy suggest disease is in more than one quadrant and patient will have a mastectomy.
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: **Ductal Carcinoma in Situ**

Variant 3: **78-year-old woman with mammographically detected 1-cm, low nuclear grade DCIS, ER-positive. Surgically excised with 5-mm negative margins. Excellent performance status, no comorbidities. Plans to take a hormonal agent for 5 years.**

Treatment	Rating	Comments
Principles of Treatment		
Adjuvant RT	8	
No RT (observation)	8	Consider observation for elderly patients or those with low-grade or negative margins.
RT Volumes		
Whole breast without boost	8	It is very reasonable to omit a boost for an elderly patient with a low-grade lesion excised with good margins.
Whole breast with boost	5	
Regional nodes	1	There is no indication for this treatment given extremely low incidence of lymph node involvement.
PBI	6	This treatment should be considered on protocol.
RT Doses (1.8–2.0 Gy/day unless otherwise specified) (Assuming widely negative margins)		
Whole breast: 42.5 Gy/16 fractions	8	This treatment is very reasonable in this elderly patient with good prognostic features.
Whole breast: 45–49 Gy	7	
Whole breast: 50–50.4 Gy	8	
Total cumulative dose, including any boost: 40 Gy	2	In this treatment, the dose is too low.
Total cumulative dose, including any boost: 50–50.4 Gy	8	
Boost dose 10 Gy in 2 Gy fractions after WBRT dose of 50 Gy	5	Consider the use of a boost dose, but the benefit is questionable.
Boost dose 16 Gy in 2 Gy fractions after WBRT dose of 50 Gy	3	In this treatment, the boost dose is too high.
Systemic Therapy		
Tamoxifen (5 years)	7	This treatment has robust data showing its efficacy.
Aromatase Inhibitor (5 years)	4	There are no data to support use of this treatment, which is pending results of clinical trials. There is minimal potential benefit in this age group. Risks and benefits must be discussed with the medical oncologist.

Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**

Clinical Condition: **Ductal Carcinoma in Situ**

Variant 4: **41-year-old premenopausal woman with mammographically detected 0.9-cm, intermediate nuclear grade, comedo DCIS, ER negative. Surgically excised with widely negative margins.**

Treatment	Rating	Comments
Principles of Treatment		
RT but no further surgery	9	
Breast MRI (after DCIS on biopsy and prior to definitive surgery)	4	Use of this treatment is unclear, but it may detect additional disease in the ipsilateral or contralateral breast, particularly in high-grade DCIS.
LN staging and RT	2	LN staging is not necessary.
No further surgery or RT (observation)	2	This treatment for a patient who is premenopausal and has a high-grade tumor is contraindicated.
RT Volumes Whole breast without boost	7	Most radiation oncologists would include a boost given the high-risk features of young age and high-grade disease despite lack of phase III data.
Whole breast with boost	8	
PBI	3	This treatment should be considered on protocol.
RT Doses (1.8–2.0 Gy/day unless otherwise specified) (Assuming widely negative margins) Whole breast: 42.5 Gy/16 fractions (without boost)	7	
Whole breast: 45 Gy	8	
Whole breast: 50–50.4 Gy	9	
Total cumulative dose, including any boost: 40 Gy	2	The dose is too low.
Boost dose 10 Gy in 2 Gy fractions (in addition to whole breast 50 Gy)	8	Most radiation oncologists would include a boost dose.
Boost dose 16 Gy in 2 Gy fractions (in addition to whole breast 50 Gy)	6	The boost dose may be higher than necessary.
Systemic Therapy Tamoxifen (5 years)	3	Consider this treatment for ER-negative disease.
Trastuzumab for 2 cycles (if HER2/neu+)	2	This treatment should be considered on protocol.
Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**		

Clinical Condition: **Ductal Carcinoma in Situ**

Variant 5: **49-year-old premenopausal woman with mammographically detected 1-cm high-grade, comedo DCIS with single focus microinvasion, ER-positive. Surgically excised with widely negative margins (>5 mm).**

Treatment	Rating	Comments
Principles of Treatment		
LN staging + adjuvant RT	9	
Mastectomy with LN staging	7	Consider this treatment if patient chooses mastectomy over BCT.
No LN staging required, proceed with adjuvant RT alone	5	Most surgeons would assess axilla surgically. Can be treated with radiation.
Mastectomy without LN staging	3	Most surgeons would perform a SLNB.
No LN staging, no adjuvant RT (observation)	1	In a premenopausal patient with high-grade disease and microinvasion, there is no role for observation.
RT Volumes (Assuming negative margins and negative SLNB)		
Postmastectomy chest wall	1	There is no indication for radiotherapy after mastectomy.
Whole breast without boost	7	Use of a boost is generally endorsed for premenopausal high-grade cases.
Whole breast with boost	8	
Regional nodes	2	There is no indication for regional nodal irradiation with a negative SLNB.
PBI	3	This treatment should be considered on protocol.
RT Doses (1.8–2.0 Gy/day unless otherwise specified) (Assuming widely negative margins)		
Whole breast: 42.5 Gy/16 fractions	8	
Whole breast: 50–50.4 Gy	8	
Total cumulative dose, including any boost: 40 Gy	2	The dose too low.
Whole breast 50 Gy + boost 10 Gy	8	
Whole breast 50 Gy + boost 16 Gy	6	This dose may be higher than necessary.
Systemic Therapy		
Tamoxifen (5 years)	8	

Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**

Clinical Condition: **Ductal Carcinoma in Situ**

Variant 6: **60-year-old woman with new microcalcifications on screening mammography. Stereotactic core biopsy shows pure pleomorphic LCIS, ER/PR negative.**

Treatment	Rating	Comments
Principles of Treatment		
Surgical excision for clear margins	7	For this treatment, rule out invasive component; biologically, the disease may behave more like high-grade DCIS than classical LCIS.
Mastectomy	5	This treatment is reasonable if clear margins cannot be achieved with lumpectomy.
Whole-breast RT	3	There is no direct evidence to support efficacy.
Observation (no surgical excision)	2	Lesions are often associated with invasive malignancy.
Surgical excision with LN staging	2	There is no indication for lymph node evaluation in the absence of invasive disease.
Systemic Therapy		
Tamoxifen (5 years)	8	This treatment is appropriate for chemoprevention regardless of hormone receptor status.
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Variant 7: **41-year-old premenopausal woman with mammographically detected 0.9-cm, high nuclear grade DCIS, plus comedo necrosis, ER negative. Surgically excised. Assume final margins >1 cm, patient wants partial breast irradiation.**

Treatment	Rating	Comments
PBI	3	This treatment should be considered on protocol.
Systemic Therapy		
Tamoxifen (5 years)	2	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Variant 8: **58-year-old postmenopausal woman with mammographically detected 1.9-cm, intermediate nuclear grade solid DCIS, ER positive. Surgically excised. Assume final margins >1 cm, patient wants partial breast irradiation.**

Treatment	Rating	Comments
PBI	6	This treatment should be considered on protocol.
Systemic Therapy		
Tamoxifen (5 years)	8	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		