Complete Summary

GUIDELINE TITLE

Ductal carcinoma in situ.

BIBLIOGRAPHIC SOURCE(S)

Rabinovitch R, Solin LJ, Shank BM, Green S, Haffty BG, Halberg FE, Mitchell SE, Strom EA, Taylor ME, White JR, Cobleigh MA, Edge SB, Mauch PM, Expert Panel on Radiation Oncology-Breast Work Group. Ductal carcinoma in situ. [online publication]. Reston (VA): American College of Radiology (ACR); 2006. 15 p. [50 references]

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Rabinovitch RA, Solin LJ, Shank BM, Haffty BG, Halberg FE, Martinez AA, McCormick B, McNeese MD, Mendenhall NP, Mitchell SE, Taylor ME, Singletary SE, Leibel S. Ductal carcinoma in situ and microinvasive disease. American College of Radiology. ACR Appropriateness Criteria. Radiology 2000 Jun;215(Suppl):1137-52.

The appropriateness criteria are reviewed annually and updated by the panels as needed, depending on introduction of new and highly significant scientific evidence.

COMPLETE SUMMARY CONTENT

SCOPE
METHODOLOGY - including Rating Scheme and Cost Analysis
RECOMMENDATIONS
EVIDENCE SUPPORTING THE RECOMMENDATIONS
BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS
QUALIFYING STATEMENTS
IMPLEMENTATION OF THE GUIDELINE
INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES
IDENTIFYING INFORMATION AND AVAILABILITY
DISCLAIMER

SCOPE

DISEASE/CONDITION(S)

Ductal carcinoma in situ (DCIS)

GUIDELINE CATEGORY

Management
Treatment

CLINICAL SPECIALTY

Internal Medicine
Oncology
Radiation Oncology
Radiology
Surgery

INTENDED USERS

Health Plans
Hospitals
Managed Care Organizations
Physicians
Utilization Management

GUIDELINE OBJECTIVE(S)

To evaluate the appropriateness of treatment procedures for patients with ductal carcinoma in situ (DCIS)

TARGET POPULATION

Women with ductal carcinoma in situ (DCIS)

INTERVENTIONS AND PRACTICES CONSIDERED

1. Mastectomy
    - With lymph node (LN) staging
    - Without LN staging
2. Lumpectomy
    - Alone
    - With radiation therapy (RT) with or without LN staging
3. Re-excision lumpectomy
    - Alone
    - With RT
    - With appropriate LN staging and RT
4. RT, including consideration volumes and doses
    - With appropriate LN staging
    - Alone, with no further surgery
5. No further surgery or RT
6. Sentinel lymph node biopsy

MAJOR OUTCOMES CONSIDERED

- Local recurrence rate

- Survival rate

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The guideline developer performed literature searches of peer-reviewed medical journals and the major applicable articles were identified and collected.

NUMBER OF SOURCE DOCUMENTS

The total number of source documents identified as the result of the literature search is not known.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Not Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not stated

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

One or two topic leaders within a panel assume the responsibility of developing an evidence table for each clinical condition, based on analysis of the current literature. These tables serve as a basis for developing a narrative specific to each clinical condition.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus (Delphi)

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Since data available from existing scientific studies are usually insufficient for meta-analysis, broad-based consensus techniques are needed for reaching agreement in the formulation of the appropriateness criteria. The American College of Radiology (ACR) Appropriateness Criteria panels use a modified Delphi

technique to arrive at consensus. Serial surveys are conducted by distributing questionnaires to consolidate expert opinions within each panel. These questionnaires are distributed to the participants along with the evidence table and narrative as developed by the topic leader(s). Questionnaires are completed by participants in their own professional setting without influence of the other members. Voting is conducted using a scoring system from 1-9, indicating the least to the most appropriate imaging examination or therapeutic procedure. The survey results are collected, tabulated in anonymous fashion, and redistributed after each round. A maximum of three rounds is conducted and opinions are unified to the highest degree possible. Eighty percent agreement is considered a consensus. This modified Delphi technique enables individual, unbiased expression, is economical, easy to understand, and relatively simple to conduct.

If consensus cannot be reached by the Delphi technique, the panel is convened and group consensus techniques are utilized. The strengths and weaknesses of each test or procedure are discussed and consensus reached whenever possible. If "No consensus" appears in the rating column, reasons for this decision are added to the comment sections.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Criteria developed by the Expert Panels are reviewed by the American College of Radiology (ACR) Committee on Appropriateness Criteria.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

ACR Appropriateness Criteria®

Clinical Condition: Ductal Carcinoma in Situ

Variant 1: 55-year-old woman with mammographically detected 2.0 cm comedo, high nuclear grade DCIS with single focus microinvasion. Surgically excised with positive deep, lateral, and medial margins.

Treatment	Appropriateness Rating	Comments
Principles of Treatment		
Mastectomy with LN staging	9	Mastectomy only if patient choice. Sentinel lymph node biopsy recommended.
Re-excision lumpectomy, appropriate LN staging, & RT if margins negative	9	
Mastectomy - no LN staging	2	
Re-excision lumpectomy & RT if margins negative	2	
Re-excision lumpectomy alone	1	
RT Volumes (Assuming negative margins)		
Whole breast +/- boost	9	
Axilla and supraclavicular fossa (s/p 1/1 macromets in SLN)	8	Completion axillary node dissection preferable.
Axilla (no LN staging performed)	3	May include within tangent fields.
Axilla and supraclavicular fossa (s/p LN staging and 1/2 micromets in SLN)	2	
Axilla (s/p LN staging, 1/7 LN+)	1	
Axilla and supraclavicular fossa (s/p LN staging and LN -)	1	
Supraclavicular fossa (s/p LN staging, LN -)	1	
RT Doses (180-200 cGy/daily fractions unless otherwise specified)		

Treatment	Appropriateness Rating	Comments
(Assuming negative margins)		
Whole breast: 4250 cGy/16 fractions	6	
Whole breast: 4500-4680 cGy/23-26 fractions	9	
Whole breast: 5000-5040 cGy/25-28 fractions	9	
Total cumulative dose, including any boost: 4000 cGy	1	
Total cumulative dose, including any boost: 4500-4680 cGy	1	
Total cumulative dose, including any boost: 5000-5040 cGy	7	
Total cumulative dose, including any boost: 6000-6600 cGy	9	
Appropriateness Criteria Scale **1 2 3 4 5 6 7 8 9** **1 = Least appropriate 9 = Most appropriate**		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

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 biopsy demonstrates DCIS with microinvasion.

Treatment	Appropriateness Rating	Comments
Principles of Treatment		
Mastectomy with LN staging	9	Sentinel lymph node biopsy recommended.
Mastectomy – no LN	2	

Treatment	Appropriateness Rating	Comments
staging		
Lumpectomy alone	1	
Lumpectomy & RT with or without LN staging	1	
Appropriateness Criteria Scale **1 2 3 4 5 6 7 8 9** **1 = Least appropriate 9 = Most appropriate**		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 3: 50-year-old woman with mammographically detected 1 cm high-grade, comedo DCIS with single focus microinvasion. Surgically excised with negative margins.

Treatment	Appropriateness Rating	Comments
Principles of Treatment		
Mastectomy with LN staging	9	Mastectomy only if patient choice. Sentinel lymph node biopsy recommended.
Appropriate LN staging + RT	9	
Mastectomy – no LN staging	2	
RT	2	
RT Volumes (Assuming negative margins)		
Whole breast +/- boost	9	
Axilla and supraclavicular fossa (s/p 1/1 macromets in SLN)	8	Completion axillary node dissection preferable.
Axilla (no LN staging performed)	3	May include within tangent fields
Axilla and	2	

Treatment	Appropriateness Rating	Comments
supraclavicular fossa (s/p LN staging and 1/2 micromets in SLN)		
Axilla (s/p LN staging, 1/7 LN+)	1	
Axilla and supraclavicular fossa (s/p LN staging and LN -)	1	
Supraclavicular fossa (s/p LN staging, LN -)	1	
RT Doses (180-200 cGy/daily fractions unless otherwise specified) (Assuming negative margins)		
Whole breast: 4250 cGy/16 fractions	6	
Whole breast: 4500-4680 cGy/23-26 fractions	9	
Whole breast: 5000-5040 cGy/25-28 fractions	9	
Total cumulative dose, including any boost: 4000 cGy	1	
Total cumulative dose, including any boost: 4500-4680 cGy	1	
Total cumulative dose, including any boost: 5000-5040 cGy	8	
Total cumulative dose, including any boost: 6000-6600 cGy	9	
Appropriateness Criteria Scale **1 2 3 4 5 6 7 8 9** **1 = Least appropriate 9 = Most appropriate**		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 4: 78-year-old woman with mammographically detected estrogen receptor (ER) positive 1 cm low nuclear grade DCIS. Surgically excised with negative margins. Plans to take Tamoxifen for 5 years.

Treatment	Appropriateness Rating	Comments
Principles of Treatment		
Mastectomy – no LN staging	8	Mastectomy only if patient choice.
RT, but no further surgery	8	
No further surgery or RT	7	
Mastectomy with LN staging	2	Sentinel lymph node biopsy only if done.
LN staging and RT	1	
RT Volumes		
Whole breast +/- boost	9	
Axilla	1	
Supraclavicular fossa	1	
RT Doses (180-200 cGy/daily fractions unless otherwise specified) (Assuming negative margins)		
Whole breast: 4250 cGy/16 fractions	6	
Whole breast: 4500-4680 cGy/23-26 fractions	9	
Whole breast: 5000-5040 cGy/25-28 fractions	9	
Total cumulative dose, including any boost: 4000 cGy	1	
Total cumulative dose, including any boost: 4500-4680 cGy	1	
Total cumulative dose,	7	

Treatment	Appropriateness Rating	Comments
including any boost: 5000-5040 cGy		
Total cumulative dose, including any boost: 6000-6600 cGy	9	
Appropriateness Criteria Scale **1 2 3 4 5 6 7 8 9** **1 = Least appropriate 9 = Most appropriate**		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 5: 60-year-old woman with mammographically detected, 1.5 cm high nuclear grade comedo DCIS. Surgically excised with positive deep, lateral, and medial margins.

Treatment	Appropriateness Rating	Comments
Principles of Treatment		
Mastectomy – no LN staging	8	
Mastectomy with LN staging	8	Sentinel lymph node biopsy recommended in setting of mastectomy in case occult invasive disease identified post facto.
Re-excision lumpectomy & RT if margins negative	8	
Re-excision lumpectomy, appropriate LN staging, & RT if margins negative	3	
Re-excision lumpectomy alone	2	
RT Volumes (Assuming negative margins)		
Whole breast +/- boost	9	
Axilla	1	

Treatment	Appropriateness Rating	Comments
Supraclavicular fossa	1	
RT Doses (180-200 cGy/daily fractions) (Assuming negative margins)		
Whole breast: 4250 cGy/16 fractions	6	
Whole breast: 4500-4680 cGy/23-26 fractions	9	
Whole breast: 5000-5040 cGy/25-28 fractions	9	
Total cumulative dose, including any boost: 4000 cGy	1	
Total cumulative dose, including any boost: 4500-4680 cGy	1	
Total cumulative dose, including any boost: 5000-5040 cGy	7	
Total cumulative dose, including any boost: 6000-6600 cGy	9	
Appropriateness Criteria Scale **1 2 3 4 5 6 7 8 9** **1 = Least appropriate 9 = Most appropriate**		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 6: 55-year-old woman with extensive pleomorphic microcalcifications in more than one quadrant on mammography. Area too large to excise with cosmetically acceptable outcome. Core biopsy demonstrates comedo DCIS.

Treatment	Appropriateness Rating	Comments
Principles of Treatment		
Mastectomy with LN staging	9	Sentinel lymph node biopsy recommended in setting of mastectomy

Treatment	Appropriateness Rating	Comments
		in case occult invasive disease identified post facto.
Mastectomy – no LN staging	2	
Lumpectomy alone	1	
Lumpectomy & RT with or without LN staging	1	
Appropriateness Criteria Scale **1 2 3 4 5 6 7 8 9** **1 = Least appropriate 9 = Most appropriate**		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 7: 45-year-old woman with mammographically detected 1 cm, high nuclear grade, comedo DCIS, ER negative. Surgically excised with negative margins.

Treatment	Appropriateness Rating	Comments
Principles of Treatment		
Mastectomy – no LN staging	8	
Mastectomy with LN staging	8	Mastectomy only if patient choice. Sentinel lymph node biopsy recommended in setting of mastectomy in case occult invasive disease identified post facto.
RT, but no further staging	8	
No further surgery or RT	2	
LN staging and RT	1	
RT Volumes (Assuming negative margins)		
Whole breast +/- boost	9	

Treatment	Appropriateness Rating	Comments
Axilla	1	
Supraclavicular fossa	1	
RT Doses (180-200 cGy/daily fractions) (Assuming negative margins)		
Whole breast: 4250 cGy/16 fractions	6	
Whole breast: 4500-4680 cGy/23-26 fractions	9	
Whole breast: 5000-5040 cGy/25-28 fractions	9	
Total cumulative dose, including any boost: 4000 cGy	1	
Total cumulative dose, including any boost: 4500-4680 cGy	1	
Total cumulative dose, including any boost: 5000-5040 cGy	7	
Total cumulative dose, including any boost: 6000-6600 cGy	9	
Appropriateness Criteria Scale **1 2 3 4 5 6 7 8 9** **1 = Least appropriate 9 = Most appropriate**		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 8: 45-year-old woman with mammographically detected 1 cm low nuclear grade, noncomedo DCIS, ER positive. Surgically excised, negative margins.

Treatment	Appropriateness Rating	Comments
Principles of Treatment		
Mastectomy – no LN	8	

Treatment	Appropriateness Rating	Comments
staging		
Mastectomy with LN staging	8	Mastectomy only if patient choice. Sentinel lymph node biopsy recommended in setting of mastectomy in case occult invasive disease identified post facto.
RT, but no further staging	8	
No further surgery or RT	4	Observation may be appropriate; consider clinical trial.
LN staging and RT	1	
RT Volumes (Assuming negative margins)		
Whole breast +/- boost	9	
Axilla	1	
Supraclavicular fossa	1	
RT Doses (180-200 cGy/daily fractions) (Assuming negative margins)		
Whole breast: 4250 cGy/16 fractions	6	
Whole breast: 4500-4680 cGy/23-26 fractions	9	
Whole breast: 5000-5040 cGy/25-28 fractions	9	
Total cumulative dose, including any boost: 4000 cGy	1	
Total cumulative dose, including any boost: 4500-4680 cGy	1	
Total cumulative dose, including any boost: 5000-5040 cGy	7	
Total cumulative dose, including any boost:	9	

Treatment	Appropriateness Rating	Comments
6000-6600 cGy		
Appropriateness Criteria Scale **1 2 3 4 5 6 7 8 9** **1 = Least appropriate 9 = Most appropriate**		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Ductal Carcinoma in Situ

Ductal carcinoma in situ (DCIS; intraductal carcinoma) is pathologically defined by the presence of carcinoma cells in well-defined ductal structures without penetration of the duct wall as seen by conventional light microscopic evaluation. Although pathologic criteria have been established for diagnosing of DCIS, there can be difficulty in distinguishing intraductal carcinoma from atypical ductal hyperplasia (at one end of the pathology spectrum) and from microinvasive carcinoma (at the other end of the pathology spectrum). Expert pathology reviews have shown significant differences in diagnosis.

Ductal carcinoma in situ can be subdivided many different ways from a clinical and pathologic perspective: palpable versus mammographic detection, architectural pattern (comedo, papillary, micropapillary, cribriform, and solid subtypes), presence or absence of comedo necrosis, nuclear grade, size, and margin status. Frequently mixed histologic subtypes may be seen.

The current treatment of DCIS remains controversial for several reasons. First, the pattern of disease presentation has changed with the increased use of mammographic screening. Lesions are now frequently detected through abnormal mammographic findings, whereas older series report predominantly palpable lesions. Second, long-term data are required to assess the efficacy of treatment, and little such data are available. Third, the few reports in the literature with long-term follow-up data have few cases. Fourth, mastectomy has been the historical standard of treatment for this disease, whereas recent interest (over the last 2 decades) has focused on breast-conservation treatment (i.e., lumpectomy with or without definitive breast irradiation). Finally, it is apparent that all DCIS is not the same. The variations in clinical and pathologic presentations and the differences in their natural histories suggest that intraductal carcinoma includes multiple subsets of disease, which in turn may require different treatments. The propensity for local recurrence is significantly greater after breast conservation treatment for comedo histologies, high-grade lesions, close or positive surgical margins, and younger patients. The difference in biology of these subtypes should therefore be factored into the decision-making process. The few completed randomized trials do not adequately address the relative impact of these various factors in a prospective manner. The remaining body of literature consists mainly of single-institution retrospective analyses.

There are three published randomized trials for DCIS evaluating breast conservation treatment issues: National Surgical Adjuvant Breast and Bowel Project (NSABP) B-17, European Organization for Research and Treatment of Cancer (EORTC) 10853, and the UK, Australia and New Zealand cooperative trial [10]. Twelve-year follow-up data are available for B-17, while the two other trials have comparatively short follow-up relative to the long natural history of this disease. Several ongoing randomized trials are attempting to address many important local and systemic therapies for the disease: Radiation Therapy Oncology Group® (RTOG) 98-04, NSABP B-35, IBIS-II, and NSABP B-39/RTOG® 0413.

There are three local treatment approaches for the breast in a woman with DCIS: 1) mastectomy; 2) excision (i.e., lumpectomy) without definitive breast irradiation; and 3) excision (i.e., lumpectomy) with definitive whole breast radiotherapy. Retrospective comparisons of the outcome of treatment for these three different treatments are problematic because of differences in patient selection.

In the setting of breast conservation, the addition of tamoxifen has potential benefit for some groups of DCIS in preventing ipsilateral breast cancer recurrence, and adds to the complexity of therapeutic decision-making. Furthermore, tamoxifen may be used as an intervention to prevent the development of contralateral breast cancer following breast conservation or a mastectomy for DCIS. Since the focus of this document is on local therapies, tamoxifen and other anti-endocrine agents will be discussed below primarily as they relate to or affect local treatment choices.

Mastectomy

Many reasons have been cited to justify the use of mastectomy as initial treatment of intraductal carcinoma. First, the rate of occult multicentricity found in the breast 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 the breast in mastectomy specimens is approximately 10%. Third, residual normal breast tissue left in the patient after breast-conservation surgery might undergo malignant transformation over time. Mastectomy essentially eliminates this possibility. Fourth, there is a risk of invasive recurrence after breast-conservation treatment, a more life threatening disease than the initial diagnosis. Furthermore, mastectomy series consistently provide the highest relapse-free survival of any treatment approach.

The reported outcome after treatment with mastectomy shows survival rates of 96%-100%. Local-regional control rates are also reported as 96%-100%. However, survival and local-regional results are virtually always reported using crude outcome calculations, not actuarial outcome calculations. The lack of actuarial outcome analyses for mastectomy series is a serious impediment to comparison with breast-conservation series. Although the reported outcomes after treatment with mastectomy are excellent, it is important to note that these results are generally not 100% survival or local-regional control, which must be considered when comparing the results of retrospective studies of mastectomy with breast-conservation treatment.

Recent emphasis on the treatment of ductal carcinoma in situ of the breast has focused on breast-conservation treatment. Prospective randomized trials have focused on the role of radiation therapy after breast-conservation surgery, the role of adjuvant tamoxifen, and the importance of pathologic subtypes of disease. No prospective, randomized trial includes a mastectomy arm. The rationale for the omission of a mastectomy arm from prospective, randomized trials is that the number of patients required to test for the potential survival advantage of 1%-3% over breast-conservation treatment would be so huge that it would be impossible to perform in practical terms. 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 breast-conservation treatment.

Management of the Axilla

There is currently no role for axillary dissection in the management of DCIS, even for high-grade or comedo lesions. Lymph node involvement has been studied in detail, and positive axillary lymph nodes are rarely seen. The risk of axillary involvement for DCIS is 0% or approaches 0% in contemporary studies. With the development of the axillary sentinal lymph node biopsy (SLNB) procedure (which entails significantly lower risk of complications than a full axillary node dissection), there has been a renewed discussion as to whether an axillary SLNB is appropriate. Due to the more detailed histopathologic evaluation of sentinel lymph nodes compared to those retrieved from an axillary dissection, reports of positive SLNBs have been described in up to 12% of cases. The clinical relevance of a positive SLNB in the setting of pure DCIS has yet to be demonstrated. As a result, SLNB is not a routine component of breast conserving surgical management of most patients with DCIS. In specific situations such as when patients are to undergo a mastectomy, an SLNB is reasonable. The logic for performing the procedure here is that should occult invasive disease be identified in the mastectomy specimen, subsequent ability to perform an SLNB procedure will have been abrogated with removal of the breast, leaving only the option for a delayed complete axillary dissection.

Breast-Conserving Therapy

The endpoints of breast-conserving therapy should be considered differently for DCIS than for invasive breast cancer. Although it is well established that mastectomy for DCIS provides the best relapse-free survival when compared with any breast-conserving therapy, this does not translate into any discernible survival advantage—although this has never been tested in a randomized trial. Breast conservation, with its known increased potential for local failure, can be a practical option for women willing to accept this difference and the subsequent interventions necessary in the event of local failure.

Excision followed by Radiotherapy

Review of single-institution data on patients treated with surgical excision followed by radiation therapy demonstrates breast failure rates of 6%-10%, although generally with relatively short follow-up. One group of researchers recently

updated the largest nonrandomized series, comprising a multi-institutional experience, 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.

Reevaluation of the pathologic material from NSABP B-06 (a randomized trial evaluating post-lumpectomy breast radiation for invasive breast cancer) revealed 76 patients who in fact had in situ and not invasive breast cancer. Local failure rates for the patients treated with excision and excision followed by radiation therapy were 43% and 7%, respectively, at a mean follow-up interval of 83 months.

Three randomized trials have been published with arms comparing excision alone with surgical excision followed by radiation therapy (with or without tamoxifen). NSABP B-17 randomized patients after lumpectomy to radiation versus no radiation (tamoxifen was not used). Twelve-year results showed that local failure was reduced from a crude rate of 31.7% without radiation to 15.7% with radiation. The inclusion criteria for this study were localized DCIS of any histology, detected either clinically or mammographically, and with negative margins following excision (no tumor on ink). The 12-year data demonstrate that radiation therapy has a greater impact on reducing the incidence of invasive recurrences, the potentially life-threatening form of recurrence (RR=.38, p=.00001), but significantly reduces non-invasive recurrences as well (RR=.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.

The EORTC 10853 trial also randomized patients after lumpectomy to radiation versus no radiation without use of tamoxifen. With a median follow-up of 51 months, local failure was 16% vs 9% in patients observed and radiated, respectively. Similar to the long term B-17 data, radiation significantly reduced invasive and DCIS recurrences in this trial. Factors that predicted for an increased local recurrence on multivariate analysis included age ≤40 years, palpable DCIS lesions, involved surgical margins, cribriform and solid histologic subtypes, and treatment with lumpectomy only.

The UK, Australia, and New Zealand (UK/ANZ) DCIS randomized trial had a more complex design in which patients were entered into a modified 2x2 randomization design after study enrollment of +/- XRT and +/- tamoxifen, or elect randomization to only +/- XRT OR +/- tamoxifen. Notwithstanding the complexity of the study design, the published results (median follow up of 52.6 months) demonstrated a reduction in ipsilateral breast cancer recurrence rates with the addition of radiotherapy (14% vs 6%, p <.0001).

All 3 trials presented above demonstrated a similar risk reduction of ipsilateral breast cancer recurrence (approximately 50%) with the addition of postlumpectomy whole breast radiotherapy, but with no impact on overall survival.

Excision Alone

The primary criticism of results from 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 adequately controlled with excision alone. Selected patients have been managed with excision alone in retrospective studies. Their criteria for consideration of excision as adequate treatment are similar: lesions detected mammographically, without a palpable component, measuring 25 mm or less and with negative margins following excision. They report local failure rates of 10%-15%. These highly selected patients treated with excision alone have demonstrated local failure rates similar to those cited in single-institution reports of surgical excision followed by radiation therapy in less rigorously selected patients. These series note that most of the breast failures were in patients with tumors of the comedo subtype. For patients treated with lumpectomy alone, one study reported that the risk of local recurrence was reduced with increasingly wide negative margins of resection. No study has reproducibly identified in a prospective fashion a subset of patients that may be treated with excision alone and have the same local recurrence rate as with excision plus irradiation.

Based on this information, and the overall impression that nuclear grade 1 and 2 tumors comprise a more favorable subset of tumors, RTOG® 98-04 is currently randomizing patients with mammographically detected DCIS after lumpectomy with at least 3 mm to the nearest surgical margin to either standard breast radiotherapy or observation. The results of ECOG E5194 evaluating lumpectomy alone for DCIS are pending.

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" (i.e., with chemotherapy or anti-endocrine therapy to treat organs beyond the breast). However, breast-conserving therapy has been improved (yet made more complex) by the recent appreciation that anti-endocrine therapy (with tamoxifen) impacts local control in the breast conservation setting. Results of B-24 demonstrated that the addition of tamoxifen (to postlumpectomy breast radiotherapy) significantly reduced ipsilateral breast tumor recurrences without an impact on survival. Recent data presented using subsets of treated patients from NSABP B-24 strongly demonstrate that the reduction of breast failure following administration of tamoxifen is limited to those DCIS lesions that are estrogen receptor (ER) positive. As a result, all DCIS lesions should undergo staining for assessment of estrogen receptor status.

Both NSABP B-35 and IBIS-II are currently accruing patients and comparing anastrazole to tamoxifen as adjuvant therapy for DCIS. At this time, there are no published data on the efficacy of any aromatase inhibitor in the adjuvant treatment of DCIS.

Microinvasive Disease (DCIS with Microinvasion)

Microinvasive carcinoma (ductal carcinoma in situ with microinvasion) is pathologically defined by the presence of early penetration of the duct wall by cancer cells beyond the basement membrane as seen by conventional light

microscopic evaluation, with no focus measuring more than 0.1 cm. Special stains are often used to assist in making the diagnosis; they can demonstrate the absence of a myoepithelial layer surrounding the tumor cells, defining a tumor that has invaded beyond the confines of a duct. Early penetration of the duct wall is commonly defined as up to 2 mm of invasion in many publications, despite the specific size criterion of $\leq$0.1 cm defined by the AJCC staging system (T1mic). The presence of unequivocal invasion is required for the diagnosis; cases with equivocal invasion are not included. Cases with up to 5 mm of invasion (T1a) are sometimes considered as having "minimal invasion" and should be distinguished from microinvasion (T1mic).

Limited information has been reported regarding treatment outcome for microinvasive carcinoma of the breast. The increasing use of screening mammography for the early detection of breast cancer has increased the number of early stage breast cancers detected. However, most studies do not report microinvasive carcinoma as a separate entity, but include this diagnosis in the earliest category of invasive disease (e.g., T1a lesions). Thus, although the diagnosis of microinvasive carcinoma is increasing, the number of reported cases, especially with long-term follow-up information, is small. There are no randomized trials that evaluate therapy for microinvasive disease.

Most investigators treat microinvasive carcinoma similarly to invasive carcinoma, not intraductal carcinoma. Microinvasive carcinoma carries a small but real risk of disease spread to axillary lymph nodes and distant metastatic sites. The reported risk of positive axillary lymph nodes is variable but is generally reported as 5%-10%, although higher and lower risks have been reported. With the development of SLNB techniques, the decision to evaluate the axilla surgically is a less difficult one, given the minimal morbidity of the procedure and the large impact a positive lymph node would potentially have on systemic management of a patient with a micro-invasive primary. Most investigators now include pathologic axillary staging (for example, with an SLNB) as a standard part of surgical management of this disease.

The options for management of the breast are 1) breast-conservation surgery plus definitive breast irradiation; or 2) mastectomy. In contrast to pure intraductal carcinoma, 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 anti-endocrine therapy. Two randomized trials were published in 2004 evaluating "elderly" women treated with or without breast radiotherapy for invasive breast cancer after lumpectomy (which presumably included but was not specifically evaluating microinvasive disease) demonstrating inferior but reasonable control rates in the group treated without radiotherapy (ranging up to 7% at 5 years).

Limited outcome data have been reported for treatment with either mastectomy or breast-conservation treatment. Reported outcomes after treatment generally show few cancer-related deaths. However, virtually no long-term actuarial outcome data have been reported. For patients selected to undergo breast-conservation treatment, acceptable local control rates have been reported. The margins of the lumpectomy specimen should preferably be negative. Definitive radiation therapy should include the whole breast (4,500-5,040 cGy in standard

fractionation), with the option of a boost to the primary tumor site bringing the total dose to 5,000-6,600 cGy. A randomized trial from Canada has demonstrated equivalent 5 year local control and cosmetic rates with a moderately accelerated whole breast dose of 4250 cGy in 16 fractions compared to standard fractionation for women with early stage invasive breast cancer. It is reasonable to consider this fractionation scheme when the standard 5-6 weeks of whole breast radiotherapy is not feasible.

Accelerated partial breast irradiation has been evaluated in several single institution and cooperative group phase II settings with acceptable early results for invasive breast cancer. Although these studies included invasive tumors up to 2-3 cm, no data are currently available specifically for the microinvasive tumor subset. A randomized phase III trial is currently accruing patients (with DCIS or invasive tumors up to 3 cm) to determine the relative efficacy and toxicity of accelerated partial breast irradiation compared to whole breast radiotherapy (NSABP B-39/RTOG 0413).

The risk of occult metastatic disease in node negative microinvasive breast cancer is very small (<5% at 10 years). Chemotherapy is therefore not used in this setting. In contrast, anti-endocrine therapy has a much lower toxicity profile; in addition to reducing the (small) risk of systemic recurrence, Tamoxifen administration will decrease the risk of ipsilateral and contralateral breast cancer in women with ER positive tumors. Anti-endocrine therapy (with tamoxifen or an aromatase inhibitor in a postmenopausal woman) is an appropriate intervention to consider for the patient with microinvasive hormone receptor-positive disease for these reasons. It is understood that the unusual patient with node positive microinvasive tumor is treated as any stage IIa breast cancer, and offered some form of systemic therapy due to a much greater risk of occult systemic disease.

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 or less. Because of the variability and interplay of breast size, tumor location, and tumor size, the decision on appropriateness of breast conservation requires joint input from both the surgeon and the radiation oncologist. Patients with extensive microcalcifications, tumor size >4-5 cm, or involvement of more than a single quadrant are appropriately treated with mastectomy. There is no role for axillary node dissection in this disease. However, in women proceeding on to 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 5-10 mm or greater) 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 4,500-5,040 cGy in standard fractionation (180-200 cGy/day), with the option for a

tumor bed boost to ensure that the total dose ranges between 5,000-6,600 cGy, depending on pathologic findings.

It remains unclear which patients are appropriate candidates for excision alone, and this continues to be an area of ongoing investigation (RTOG® 98-04). The addition of tamoxifen in a hormone receptor positive DCIS patient should be considered.

At the time of this writing, NSABP B-39/RTOG® 0413, NSABP B-35, RTOG® 9804, and IBIS-II are all open to accrual for patients with DCIS of the breast.

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 the 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 to a total dose of 4,500-5,040 cGy in standard fractionation, with the option for a tumor bed boost to ensure that the total dose ranges between 5,000-6,600 cGy, 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 anti-endocrine therapy is being considered.

Abbreviations

- DCIS, ductal carcinoma in situ
- LN, lymph node
- RT, radiotherapy
- SLN, sentinel lymph node
- s/p, status post

CLINICAL ALGORITHM(S)

Algorithms were not developed from criteria guidelines.

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are based on analysis of the current literature and expert panel consensus.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate management of patients with ductal carcinoma in situ (DCIS)

POTENTIAL HARMS

Not stated

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

An American College of Radiology (ACR) Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists, and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those exams generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the U.S. Food and Drug Administration (FDA) have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Personal Digital Assistant (PDA) Downloads

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Rabinovitch R, Solin LJ, Shank BM, Green S, Haffty BG, Halberg FE, Mitchell SE, Strom EA, Taylor ME, White JR, Cobleigh MA, Edge SB, Mauch PM, Expert Panel on Radiation Oncology-Breast Work Group. Ductal carcinoma in situ. [online publication]. Reston (VA): American College of Radiology (ACR); 2006. 15 p. [50 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1996 (revised 2006)

GUIDELINE DEVELOPER(S)

American College of Radiology - Medical Specialty Society

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GUIDELINE COMMITTEE

Committee on Appropriateness Criteria, Expert Panel on Radiation Oncology – Breast Work Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Rabinovitch RA, Solin LJ, Shank BM, Haffty BG, Halberg FE, Martinez AA, McCormick B, McNeese MD, Mendenhall NP, Mitchell SE, Taylor ME, Singletary SE, Leibel S. Ductal carcinoma in situ and microinvasive disease. American College of Radiology. ACR Appropriateness Criteria. Radiology 2000 Jun;215(Suppl):1137-52.

The appropriateness criteria are reviewed annually and updated by the panels as needed, depending on introduction of new and highly significant scientific evidence.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the American College of Radiology (ACR) Web site.

ACR Appropriateness Criteria® *Anytime*, *Anywhere*™ (PDA application). Available from the ACR Web site.

Print copies: Available from the American College of Radiology, 1891 Preston White Drive, Reston, VA 20191. Telephone: (703) 648-8900.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- ACR Appropriateness Criteria®. Background and development. Reston (VA): American College of Radiology; 2 p. Electronic copies: Available in Portable Document Format (PDF) from the American College of Radiology (ACR) Web site.

PATIENT RESOURCES

None available

NGC STATUS

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