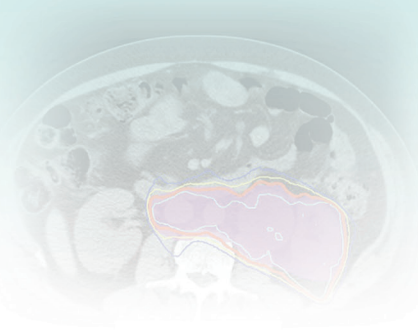
CHAPTER

62 Noninvasive Breast Cancer



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INCIDENCE

Noninvasive breast disease accounts for more than 20% of all breast cancers. Lobular carcinoma in situ (LCIS) represents less than 15% of these noninvasive cancers, whereas ductal carcinoma in situ (DCIS) represents 85% of noninvasive cancers. A third less common form of noninvasive disease, Paget's disease, accounts for 0.5% to 5% of all breast cancers.

BIOLOGIC AND PATHOLOGIC CHARACTERISTICS

LCIS is a noninfiltrating lobular proliferation exemplified by loose discohesive cells filling the acinar space. Lesions are frequently positive for estrogen receptor (ER) and progesterone receptor (PR), and loss of *E-cadherin (CDH1)* gene expression is characteristic. Overexpression of the c-*ERBB2* gene or mutation of the *TP53* gene may occur, but this is rare with the exception of pleomorphic LCIS.

In Paget's disease, Paget's cells are found in the epidermis with underlying malignant tissue found in more than 95% of cases.

DCIS is a noninfiltrating clonal proliferative process confined to the ductal lumens of the breast. DCIS may be a precursor to invasive disease. ER positivity is present in 70% of DCIS lesions; the rate of expression varies according to the grade of the lesion. The rate of expression is 90% in low-grade lesions and 25% in high-grade lesions. About 35% of DCIS lesions exhibit overexpression of the *HER2 (ERBB2)* gene and about 25% exhibit mutation of the *TP53* tumor suppressor gene.

STAGING AND EVALUATION

Staging and evaluation are accomplished with bilateral mammograms and excision with pathologic evaluation, which should determine the size and histologic type of the lesion, the ER and PR status, and the lesion's margin status. MRI is increasingly being used to help identify women with multicentric disease and those ineligible for breast-conserving therapy. In LCIS, the pathologic evaluation is limited to identification of the lesion and ER and PR status.

TREATMENT

For LCIS, treatment usually consists of observation. The rate of in-breast failure at 12 years is less than 15%. LCIS has a minimal impact on survival rates. Alternative approaches for high-risk disease have included tamoxifen versus bilateral mastectomy.

Treatment for Paget's disease usually involves breast-conserving therapy. Excision with negative margins is needed, followed by whole-breast radiotherapy. In-breast control rates are 87% to 95%. Patients with high-risk disease (i.e., diffuse disease with positive margins despite reexcision) should undergo mastectomy.

Breast-conservation therapy is also recommended for DCIS lesions. Excision with negative margins is followed by whole-breast radiation therapy with in-breast control rates of 85% to 95%. For low-risk disease (i.e., grade I lesions of <1 cm and negative margins of >1 cm), excision alone may be chosen. Mastectomy may be used for high-risk disease (i.e., diffuse disease with positive margins despite reexcision). More recently, data supporting the use of shortened radiation schedules as part of breast conservation has emerged in the form of accelerated partial breast irradiation and hypofractionated whole-breast irradiation.

INTRODUCTION

Noninvasive breast cancer is composed of three distinct histologic entities: LCIS, Paget's disease, and DCIS. As a result of the increased quality of and use of mammography, these three histologic types make up a larger percentage of all the breast cancer cases seen today.[1] Historically, mastectomy was frequently used as treatment for noninvasive disease, but with a better understanding of the natural history of these noninvasive disease processes, investigation has led to breast-conserving treatment options with regards to DCIS and Paget's disease and observation or risk-reduction for LCIS. Controversy regarding the optimal treatment approach continues to exist, and as a result, treatment recommendations range from observation to breast-conservation therapy to mastectomy. To appropriately formulate a patient's treatment options, it is important to understand the distinguishing pathologic appearances, biologic characteristics, and natural history of these three noninvasive breast disease entities.

LOBULAR CARCINOMA IN SITU

LCIS was first described as a pathologic entity by Foote and Stewart in 1941.[2] Microscopically, LCIS appears as a noninfiltrating process of lobular proliferation. LCIS has been reported to present with multicentric breast involvement in up to 90% of mastectomy specimens, with bilateral involvement documented in 35% to 59%.[3-6] Histologically, LCIS is characterized by loose discohesive epithelial cells filling the acinar space.[3-6] The degree of lobular involvement ranges from a simple filling of the ductal lumens to moderate distention to overt distention with extension into the adjacent extralobular ducts.[7] As a result of this spectrum of appearances, the lines of histologic delineation can become blurred between atypical ductal hyperplasia, LCIS, and when ductal extension is seen, DCIS. This introduces a source of complexity when comparing publications from varying institutions; even when using a proposed three-tier grading system, controversy still exists.[4-6,8]

Molecular markers have been suggested as a potential method of providing a technique for distinguishing LCIS in problematic cases.[5] LCIS cells are frequently ER-positive cells, and rarely overexpress c-ERBB2 or contain p53 mutations, with the exception of pleomorphic LCIS, which expresses high rates of Ki-67 and p53 positivity.[5,9-12] The loss of *CDH1* gene expression is documented in more than 95% of LCIS cases.[11,13] The *CDH1*gene is a calcium-dependent cellular adhesion molecule that is responsible for epithelial organization, and the absence of this adhesion molecule in LCIS may explain its discohesive morphologic characteristics.[11,13]

Publications on biopsy results report LCIS incidence rates to be 0.5% to 3.6%; these lesions represent less than 15% of all noninvasive lesions recorded, but recent population-based analyses suggest that this rate may be increasing.[6,14,15] Because there are no clinical or mammographic indicators, LCIS without additional histologic findings is typically an incidental finding when biopsy is performed for alternative reasons.[2-5,14] Although mammographically detected calcifications corresponding with LCIS have been reported, the calcifications are more commonly unassociated and are present in the adjacent tissue; therefore, if LCIS is identified on biopsy with a mammogram demonstrating calcification excisional biopsy is warranted.[14,16] In fact, DCIS or invasive disease, or both, is frequently identified in the subsequent lumpectomies performed (22% to 27% of cases) when LCIS is the sole histologic entity seen on core biopsy.[12,17,18] Criteria identifying those patients for whom observation only is sufficient following core biopsy showing LCIS have not yet been clearly specified.

Management considerations for LCIS differ depending on whether it is associated with a diagnosis of DCIS or infiltrative disease or whether LCIS is the sole histologic entity encountered. Only 5% to 12% of early-stage breast cancers have an associated component of LCIS.[19,20] Several institutional experiences have evaluated the potential impact of the presence of LCIS on breast-conserving treatment outcomes.[19-24] The number of patients included in these experiences is relatively small, and there are differences in these cohorts, including pathologic assessment, length of follow-up, and use of tamoxifen (Table 62-1). However, the majority of data suggest that no statistically significant difference exists when comparing rates of in-breast disease control, distant disease-free survival, and overall survival between patients with or without a component of LCIS.[19-24] The presently accepted treatment approach is to manage the breast according to the dominant histologic findings present (DCIS or invasive disease) and disregard the presence of LCIS. Additional surgery is not pursued to obtain LCIS clear margins. The need for the addition of tamoxifen or a more aggressive treatment approach in this group of high-risk patients is uncertain, and further study is necessary with no definitive evidence-based guidelines available.[25]

If LCIS is the sole histologic diagnosis, treatment recommendations range from observation to mastectomy. When first described as a pathologic entity, the significance of LCIS was unknown and mastectomy was consistently pursued.[2] Knowledge of frequent contralateral involvement extended treatment recommendations to random contralateral biopsy and bilateral mastectomy.[2,3] However, observational studies after lumpectomy only have led to a better understanding of the natural history of this disease, and a more conservative approach is now commonly practiced.[6,14] Although studies of *CDH1* and loss of heterozygosity (LOH) suggest that LCIS may be a precursor to invasive disease, LCIS has historically been considered a marker for an increased risk of developing invasive disease (9 to 12 times that of the normal population); this risk requires long-term follow-up exceeding 20 years.[4,26] More recently, population based data has found that 73% of patients undergo excision alone, 16% mastectomy, 10% biopsy, and 1% excision with radiation therapy.[15]

A range of ipsilateral and contralateral breast failure rates are reported following treatment. This variation is the result, in part, of differences in the length of follow-up, the definitions used for histologic classification (atypical lobular hyperplasia versus LCIS), and the extent of excision used in these observational studies.[27,28] In a 12-year follow-up publication on a 182-patient cohort treated with lumpectomy only for LCIS, the National Surgical Adjuvant Breast and Bowel Project (NSABP) reported a 14.4% in-breast tumor recurrence (IBTR) rate, and a 7.8% contralateral breast tumor recurrence (CBTR) rate.[28] Of the IBTRs, nine (34.6%, or 5% of the total cohort) were invasive malignant tumors and 17 (65.4%, or 9% of the total cohort) were noninvasive malignant tumors. Although the frequency of CBTRs was less than that of IBTRs, the frequency of invasive CBTRs (5.6% of the total cohort) was similar to that of invasive IBTRs (5% of the total cohort). All of the IBTRs were documented to be at the site of the index lesion except for one, characterized as pure LCIS, that was found at a remote site. This report continues to support the indolent nature of LCIS and a conservative management approach.

The impact of subsequent development of invasive disease on mortality risk has been estimated in earlier publications to

TABLE 62-1 Presence of LCIS versus in-Breast Failures in Breast-Conservation Therapy

Author	Median Follow-up Time	Disease Stage	No. Patients		Tamoxifen		In-Breast Failure Rate (%) at 10 yrs		*p* Value
			Positive for LCIS	Negative for LCIS	LCIS-Positive Receiving Tamoxifen (%)	LCIS-Negative Not Receiving Tamoxifen (%)	Positive for LCIS	Negative for LCIS	
Abner et al[19]	13.4 yrs	I-II	137	1062	2 overall		13*	12*	NS
Moran et al[20]	10.6 yrs	0-II	51	1045	20	20	23	17	NS
Jolly et al[21]	8.7 yrs	I-II	56	551	54	35	14	7	0.04
Sasson et al[22]	6.3 yrs	I-II	65	1208	40	35	29	6	0.0003
Ciocca et al[23]	6 yrs	0-II	290	2604	63.5	44.6	6	6	NS
Ben-David et al[24]	3.9 yrs	0-II	64	121 (matched pair)	48.5	39	0.9†	0†	NS

LCIS, *Lobular carcinoma in situ;* NS, *not statistically significant;* yrs, *years.*

**8 years.*

†5 years.

be 5% to 7% with a population study identifying the risk at 7.1% at 10 years.[14,29] However, with contemporary use of close mammographic and clinical follow-up leading to early detection of subclinical abnormalities, one would expect this mortality risk to be reduced. This reduction is reflected in the lower mortality risk (1%) reported by the NSABP.[28] Further, recent guidelines have not suggested an alteration in subsequent screening in those diagnosed with LCIS further supporting the reduced risk of mortality.[25]

Management options vary depending on individual risk assessment (Figure 62-1). Close observation with regular physical examinations and mammographic surveillance is the accepted management approach.[6,14,25,27,28] At present, there is no role for radiotherapy in the management of LCIS. Knowing that this is a bilateral breast disease process leaves a unilateral treatment approach inadequate (i.e., ipsilateral mastectomy).[25] Bilateral prophylactic mastectomy is thought to be excessive in all patients except those believed to be at higher risk (i.e., young patients, diffuse process, a significant family history of disease) for whom it could be considered.[25] A less radical approach to be considered is the use of tamoxifen. Indeed, a cohort of patients with LCIS was entered into the NSABP P-01 trial, which compared tamoxifen with placebo for breast cancer prevention. The 5-year risk of subsequent disease development was reduced with the use of tamoxifen by 56%, though patients with LCIS represented a small percentage of patients.[30]

Pleomorphic LCIS represents an emerging area of interest based on data demonstrating differences in molecular markers for this variant as well concern for underlying invasive malignancy with further sampling.[12,31] Data from Northwestern University found that variants of LCIS including pleomorphic LCIS were misinterpreted as solid DCIS in up to 15% of cases and that 20% of such cases had underlying lobular carcinoma at the time of surgery, which has been confirmed by other series.[31,32]

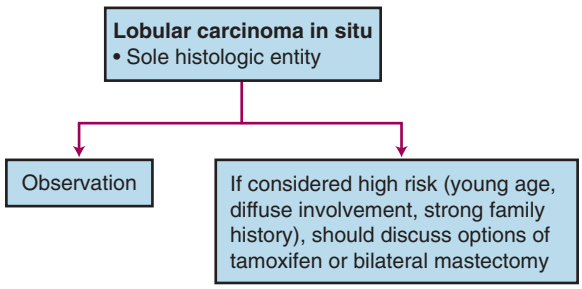

Figure 62-1 Treatment algorithm for lobular carcinoma in situ.

PAGET'S DISEASE

The clinical presentation of crusting, bleeding, and ulceration of the nipple was first described in 1856, but it was not until 1874 that the association with an underlying breast carcinoma was recognized by Sir James Paget.[33] Paget's disease of the nipple is characterized histologically by the presence of unique, clearly identifiable Paget's cells that are described as large, round to oval cells that contain hyperchromatic nuclei and prominent nucleoli with frequent mitoses noted. The Paget's cells occur singly or in clusters and are scattered throughout the epidermis.[34,35]

Reported in 0.5% to 5% of breast cancer patients, Paget's disease is an infrequent diagnosis.[33,36,37] It is most commonly unilateral, but reports of bilateral and male Paget's disease can be found.[38-40] Clinically, women describe itching and burning of the nipple and areola and crusting is often described. There is a slow progression toward an eczematoid appearance, which can extend to the skin. If neglected, bleeding, pain, and ulceration can occur.[37,38] The differential diagnosis includes superficial spreading melanoma, pagetoid squamous cell carcinoma in situ, and clear cells of Toker.[34-37] A palpable mass is detected in about 50% of patients at diagnosis. If there is a palpable mass, more than 90% will be invasive carcinoma. On the other hand, if no palpable mass is detected, 66% to 86% will have an underlying DCIS.[34-37] These adjacent, underlying malignant tumors are usually located centrally; however, they have also been located elsewhere in the breast.[33,37]

The appropriate management of Paget's disease remains unsettled; however, in concordance with physician and patient preference, attempts have been made to investigate the role of breast-conservation therapy. Because mastectomy was initially shown to be effective, the transition to breast-conserving treatment has been done cautiously because of the inability to accumulate a significant number of uniform patients similarly treated.[36,37] Recent data have demonstrated that based on pathological evaluation of mastectomy specimens, that breast-conserving therapy is feasible with appropriate margins and this is echoed in currently published treatment guidelines.[25,41] Limited series have described results with various forms of breast-conserving treatment, including limited surgical resection alone, radiotherapy alone, and limited resection followed by radiotherapy[42-47] (Table 62-2).

The combination of limited surgical resection and postoperative radiotherapy appears to be the most successful breast-conservation approach. Two collaborative studies have shown the successful use of breast-conservation therapy in Paget's disease of the nipple. The European Organization for Research and Treatment of Cancer (EORTC) Study 10873 was a

TABLE 62-2 Breast Conservation in Treatment of Paget's Disease

Author	No. Patients	Median Follow-up Time	Treatment Approach	Palpable Mass		DCIS Only		Actuarial Local Control Rate at 5 yrs
				Yes	No	With	Without	
Polgar et al[43]	33	6 yrs	Cone excision alone	91	9	91	9	71.6%
Stockdale et al[44]	19	5 yrs, 3 mos	Radiotherapy alone	30	3	30	3	84.2% (crude)
Bijker et al[45]	61	6.4 yrs	Cone excision + radiotherapy	3	97	93	7	94.8%
Pierce et al[46]	30	5.2	Excision + radiotherapy	59	2	57	4	91%
Marshall et al[47]	36	9.4 yrs	Excision* + radiotherapy	0	36	27	3†	91% (5-yr)‡ 87% (10-yr)‡ 87% (15-yr)‡

DCIS, *Ductal carcinoma in situ;* mos, *months;* yrs, *years.*
**Final margin status: 56% negative, 6% positive, 39% unknown.*
†6% DCIS and invasive disease, 3% invasive disease only, 16% no underlying pathology.
‡Breast as only site of failure.

multiinstitutional registration study reporting a 5-year local recurrence rate of 5.2% for a subset of 61 patients.[45] In this study, a complete excision with tumor-free margins of the nipple-areolar complex and underlying breast tissue was followed by whole-breast radiotherapy to 50 Gy. The median follow-up time was 6.4 years, and the majority of patients were found to have an underlying DCIS without a palpable mass.

The second study, a seven-institution collaborative review of 36 patients, included patients with Paget's disease without a palpable mass or mammographic density.[47] The median follow-up time was 9.4 years, and all had at least 12 months of follow-up. Patients underwent complete (69%) or partial (25%) excision of the nipple-areolar complex and underlying breast tissue, with 6% reported as a biopsy only. The final margin status was documented as negative in 56%, positive in 6%, and unknown in 39%. All received whole-breast irradiation at a median dose of 50 Gy, and the majority received an additional boost dose to the tumor bed. Actuarial rates of local in-breast failure as the only site of first recurrence were 9% at 5 years and 13% at both 10 years and 15 years. Despite the variation of clinical, pathologic, and treatment factors, statistical evaluation did not identify any factors that significantly predicted for risk of local recurrence. The findings from these studies have been confirmed by a large series from Sweden that evaluated 223 patients and found that type of surgery (BCS versus mastectomy) was not associated with breast cancer survival or disease free survival.[48]

On presentation, the workup and evaluation should include a bilateral breast examination, mammography, and full-thickness biopsy to confirm the diagnosis of Paget's disease and fully evaluate the extent of the underlying malignant disease.[25] In individuals with a positive biopsy for Paget's but no underlying mass, consideration for magnetic resonance imaging (MRI) is reasonable.[25] An individual's prognosis is not dependent on the diagnosis of Paget's disease but rather depends on the associated underlying malignant disease. Therefore, local treatment decisions as well as systemic and regional nodal disease risk management should be based on the underlying disease (Figure 62-2).[25] Standard breast-conservation therapy principles governing patient selection, surgical resection, and radiotherapy should be applied. Complete surgical resection of the disease process (i.e., nipple-areolar complex excision in conjunction with any underlying disease) with a negative microscopic surgical margin is then followed by standard whole-breast irradiation.

DUCTAL CARCINOMA IN SITU

Epidemiology

DCIS is represented by a heterogeneous spectrum of histologic appearances that all arise within and are confined to the ductal lumens of the breast. This clonal proliferation does not breach the epithelial basement membrane, and there is no evidence of invasion into the adjacent breast stroma.[49] DCIS lacks the ability to metastasize; the rarely reported axillary nodal metastasis or distant metastasis has been attributed to the probable presence of an undetected component of invasive carcinoma.[49,50]

Before 1980, the incidence of DCIS was low (i.e., only 1.4% of all breast biopsies and only 5% of all breast malignant tumors).[51,52] With the increased use of mammography and as pathologists began to recognize that DCIS was a distinct pathologic entity, the incidence of DCIS dramatically increased.[53] The incidence of DCIS has increased from 4800 cases reported in 1983 to more than 50,000 cases out of the estimated 230,000 new breast cancers diagnosed in 2013.[53] With this increase, there has been a corresponding change in the presentation of DCIS lesions from predominantly palpable to more than 90% of new lesions being nonpalpable.[54] Studies have shown that the rate of DCIS lesions detected by screening increases with age, whereas DCIS accounts for a progressively smaller percentage of the total cancers detected (i.e., invasive cancers plus DCIS).[55,56] The rate of DCIS detection has been shown to increase from 0.56 per 1000 mammograms among women aged 40 years to 49 years to 1.07 per 1000 mammograms among women aged 70 years to 84 years.[56]

Associated risk factors for the development of DCIS are similar to risk factors for invasive disease and include older age, benign breast disease, mammographic density, a family history of breast disease, and reproductive factors, including nulliparity or older age of pregnancy.[49,57-59]

Prevention and Early Detection (MRI)

Although successful treatment options are available, improved outcomes can be realized through both prevention of DCIS development and the early detection of new lesions. The role of tamoxifen in the prevention of disease development has been studied by the NSABP in a protocol that randomized patients at high risk for the development of breast cancer to either tamoxifen or placebo.[30] Patients eligible included those who were either 60 years of age or older, had a history of LCIS, or were between the ages of 35 and 59 years with a

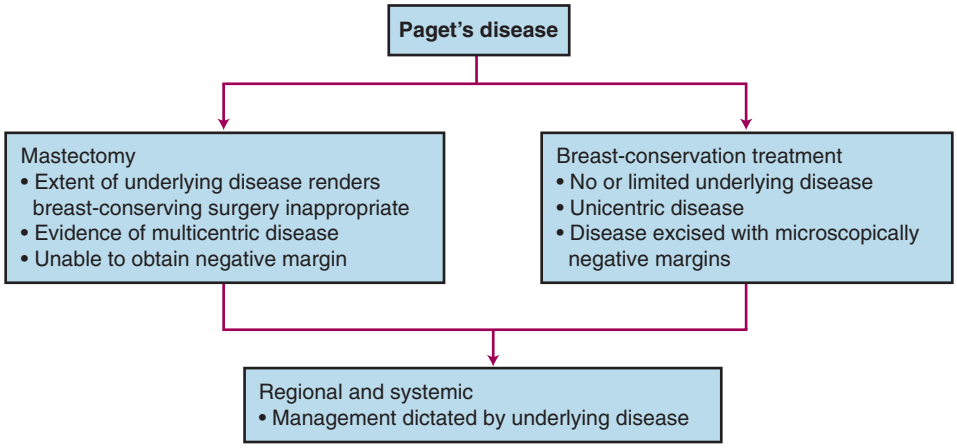

Figure 62-2 Treatment algorithm for Paget's disease.

5-year predicted risk for breast cancer, using the Gail model, of at least 1.66%. The 7-year follow-up data reveal that for noninvasive breast cancer, tamoxifen use was associated with a 37% reduction in risk. A subsequent randomized trial (NSABP P-2) randomized similar patients (woman who were premenopausal excluded) to tamoxifen or raloxifene. At 5 years, raloxifene was found to have a statistically nonsignificant increase in the incidence of noninvasive cancers than tamoxifen (relative risk, 1.40).[60]

Mammography plays an essential role in the early detection of noninvasive lesions, providing an opportunity for intervention early in the course of disease development. The distinctive mammographic feature of DCIS is the presence of microcalcifications, which has been reported in 84% to 98% of cases.[61,62] Seventy-two percent to 76% of DCIS lesions have microcalcifications as the sole mammographic finding, and an additional 12% have microcalcifications in combination with other mammographic abnormalities.[61,62] Beyond detection, several attempts have been made to correlate the mammographic appearance of the lesion with the histologic type, grade, and extent of disease. Linear branching microcalcifications have been reported to be associated with high-grade or comedo-type DCIS. Heterogeneous granular calcification is commonly associated with moderately differentiated DCIS and fine granular microcalcifications more typically with low-grade, non-comedo DCIS.[56,61,62] Although there is a degree of correlation between appearance and histologic type, there is considerable overlap, which limits the use of this information in clinical decision making. Microcalcifications are not always present throughout the histologic abnormality, and the estimated mammographic size and extent of disease frequently underestimate the true pathologic extent of the disease process. Although the mammographic extent can be used to guide the extent of surgical excision, caution should be exercised because the size is typically underestimated by 1 cm to 2 cm.[63,64] In patients presenting with nipple discharge with a negative mammographic evaluation, galactography may be helpful in distinguishing the presence of a papilloma from an underlying DCIS.[65]

More recently, MRI has emerged as another modality to help identify lesions. Its use has been suggested in patients with dense breasts as well as to identify multicentric disease and is increasingly being used in the noninvasive setting.[25] Further, recent studies have found that MRI has increased sensitivity to detect DCIS compared with mammography and can better identify those patients eligible for BCT.[66]

Biologic Characteristics and Molecular Markers

DCIS is a precursor lesion to invasive ductal carcinoma and exists along an evolutionary continuum that starts with benign breast tissue and ends with an invasive breast lesion.[67] This concept has been verified in several ways. For years, pathologists have recognized and documented confirmation of a histologic progression from benign breast cells to invasive breast cancer and realized that this histologic evidence was more commonly present where an invasive lesion was discovered. The evolutionary concept is further supported by the acknowledged association between the presence of DCIS and the subsequent increased risk of developing an invasive breast cancer.[49,68,69] In some series, a 10-fold risk of developing an invasive lesion has been reported. The presence of shared identical genetic abnormalities between DCIS and synchronous invasive breast cancer also suggests a clonal relationship of biologic progression.[49,68-70] This was noted in a recent study that found that the molecular phenotypes of coexisting DCIS within IDC were identical in 100% of cases.[71]

Documented genetic and molecular differences can differentiate DCIS from normal breast tissue. Genetic alterations have been evaluated with an analysis of LOH that has demonstrated gain or loss of multiple loci.[68-70] LOH is not seen in normal breast tissue but is present with an increasing frequency that correlates with histologic progression from benign to malignant tissue. In hyperplasias from noncancerous breasts, LOH is rarely documented; however, it is more commonly present (in 42% to 50% of patients) in atypical ductal hyperplasia. Among specimens harvested from cancerous breasts, 77% of noncomedo and 80% of comedo DCIS lesions share LOH with the synchronous invasive lesion in at least one locus.[70] Molecular markers have been studied and are found to have a heterogeneous distribution of expression.[49] The ER is present in 65% to 80% of DCIS lesions, but the rate of expression is high (90%) in low-grade lesions and is significantly less (25%) in high-grade lesions.[49,72] This trend is reversed with the *HER2/neu* proto-oncogene and the *TP53* tumor suppression gene. About 25% to 50% of DCIS lesions exhibit overexpression of the *HER2/neu*, with the *TP53* tumor suppressor gene mutated in 25% of cases. Both of these molecular markers are noted in less than 20% of low-grade lesions, but they are found in up to two thirds of high-grade lesions.[49,72]

Pathologic Characteristics and Pathways of Spread

The primary goal of pathologic assessment is to differentiate DCIS from invasive cancer because the presence of invasive disease alters the focus of treatment from the breast only to possible regional and distant metastases. Once DCIS has been identified, pathologic classification follows in an attempt to predict the clinical outcome and direct the treatment management. Historically, an architectural classification system has been used, dividing tumors into the five classic subtypes of comedo, solid, cribriform, papillary, and micropapillary cancers.[73-75] Less common subtypes have been described and include apocrine, neuroendocrine, signet-ring cell cystic, and hypersecretory carcinomas and clinging DCIS.[76] The difficulty with an architectural classification method is that there can be a mixture of architectural subtypes identified within the same lesion and that the reproducibility of classification is unreliable because pathologists apply various criteria.[77,78] Additionally, the value of an architectural classification system is questionable because the architectural subtypes do not correlate well with clinical behavior.[79] Although this was not an issue when mastectomy was routinely used, the ability to predict clinical behavior has become important now that breast-conserving approaches represent the standard of care in the management of DCIS.[25]

In an attempt to better predict clinical behavior, several classification systems have been proposed.[80,81] These are based on nuclear grade of the tumor cells and presence of comedo necrosis with and without architectural features. These characteristics appear to correlate with the risk of local recurrence.[79] In 1997, an international consensus conference was convened to discuss several pathologic aspects concerning DCIS, with the goal of reaching a consensus where possible.[82] Conference participants recognized that several classification systems had been proposed, and although a specific system was not endorsed, they recommended that four features be routinely described: nuclear grade, necrosis, polarization, and architectural pattern. They also recommended that several additional features be documented in the pathology report, including the margin status, size of the lesion, location of microcalcification in relationship to the DCIS lesion, and correlation of characteristics of the tissue specimen with radiographic and mammographic findings.[82]

Primary Therapy

Patient evaluation focuses on bilateral mammography, with which the presence of additional breast malignant lesions can be excluded and the extent of the DCIS process defined; MRI may also be useful to determine extent of disease and any multifocality or multicentricity.[25] After it is determined that DCIS is the only disease entity requiring treatment, the primary focus becomes local management of the breast. In concert with the spectrum of clinical presentations encountered with DCIS, there are several treatment approaches. They range from treatment of the whole breast to treatment of a partial breast target. On the one end of this spectrum, when multicentric disease or a diffuse DCIS process is documented, a mastectomy is considered to be the standard of care.[25] If a focal area of DCIS is confronted, then breast-conserving approaches are favored because of improved quality-of-life outcomes. Supported with Phase III trial data, the use of standard breast-conservation therapy with lumpectomy and standard whole-breast radiotherapy is most commonly recommended, and newer partial breast techniques (with and without radiotherapy) are now being offered with increased frequency based on emerging data.

All presentations of DCIS can be successfully managed with total mastectomy. This is supported by reports from mastectomy series showing disease control rates that approach 100% and cancer-specific mortality rates of less than 4%.[83-86] However, it is recognized that the availability of mammographic screening has shifted the most common presentation of DCIS from one of a palpable mass with advanced involvement to one of early-stage and limited-extent of disease for which a total mastectomy would intuitively appear to be excessive.[25,49] To promote mastectomy in the management of noninvasive disease would be in opposition to the increasing use of breast-conservation therapy for invasive disease. Although a Phase III trial comparing total mastectomy with breast-conservation therapy for DCIS has never been done, the psychological benefits of preserving the breast and the acceptable rates of local control achieved with breast-conserving therapy support the use of total mastectomy only when necessary. Total mastectomy is most commonly reserved for patients presenting with multicentric or diffuse disease, for patients in whom the use of radiotherapy is contraindicated, when an unacceptable cosmetic result is anticipated following appropriate surgical excision, or for salvage in the event of in-breast recurrence following standard breast-conservation therapy.[25,87]

Breast-conservation treatment consists of initial surgical excision of the primary lesion with a negative surgical margin followed by whole-breast radiotherapy delivered with standard accepted techniques, such as those used for early-stage invasive breast cancer. Literature supporting this approach is found both in retrospective series as well as in prospective Phase III trials comparing lumpectomy only with lumpectomy followed by whole-breast irradiation.[88-92]

Retrospective analyses of lumpectomy and whole-breast irradiation have reported 5-year cause-specific survival rates that approach 100% and local control rates that range from 85% to 95%.[88,93-98] Prospective randomized trials have been completed evaluating the role of postoperative radiotherapy and tamoxifen in breast-conserving management of DCIS (Tables 62-3 and 62-4). In a Cochrane Database review, postoperative radiotherapy for DCIS focused on four prospective randomized trials[99] (see Table 62-3). This meta-analysis confirmed a statistically significant benefit from the addition of radiotherapy for all ipsilateral breast events (hazard ratio [HR], 0.49; $p < 0.00001$), for DCIS (HR, 0.61; $p = 0.03$), and for invasive recurrence (HR, 0.50; $p = 0.0001$). This benefit was demonstrated in all of the subgroups evaluated, which included patients who underwent complete excision versus those who underwent incomplete excision, patients older than 50 years versus those younger than 50 years, patients with comedo necrosis versus those without comedo necrosis, and patients with lesions of 1 cm or larger versus those with lesions of less than 1 cm; these findings have also been confirmed by the Early Breast Cancer Trialists Group meta-analysis.[100]

The first of these four prospective randomized trials is the National Surgical Adjuvant Breast and Bowel Project (NSABP)

TABLE 62-3 Randomized Clinical Trials Evaluating the Role of Postoperative Radiotherapy in the Management of DCIS

			Local Recurrence (Cumulative %)				Overall Survival (%)		
Trial Group	No. Patients	Follow-up Time	Histologic Type of Recurrent Disease	Lumpectomy	Lumpectomy + Postoperative Radiation Therapy	*p* Value	Lumpectomy	Lumpectomy + Postoperative Radiation Therapy	*p* Value
NSABP B-17[89]	818	15-yr actuarial	DCIS	15.4	9.0	<0.001	84.2	82.9	NS
			Invasive	19.6	10.7	<0.001			
			DCIS + invasive	35.0	19.8	—			
EORTC 10853[90]	1010	15.8-yr median	DCIS	16.0	8.0	0.003	90	88	0.93
			Invasive	16.0	10.0	0.007			
			DCIS + invasive	31.0	18.0	<0.001			
UKCCCR[91]	1030	12.7-yr median	DCIS	9.7	3.8	<0.0001	90%	90%	—
			Invasive	9.1	3.3	<0.0001			
			DCIS + invasive	19.4	7.1	<0.0001			
SweDCIS[92]	1067	20-yr	DCIS	Absolute Difference: 10%		—			—
			Invasive	Absolute Difference: 2%		—			
			DCIS + invasive	Absolute Difference: 12%		—			

DCIS, *Ductal carcinoma in situ;* EORTC, *European Organization for Research and Treatment of Cancer;* NSABP, *National Surgical Adjuvant Bowel and Breast Project;* SweDCIS, *Sweden Breast Cancer Group DCIS trial;* UKCCR, *United Kingdom Coordinating Committee on Cancer Research;* yr, *year.*

TABLE 62-4 Randomized Clinical Trials Evaluating the Role of Tamoxifen in the Management of DCIS

Trial Group	No. Patients	Follow-up Time	Local Recurrence (Cumulative %)				Contralateral Recurrence (%)		
			Histologic Type of Recurrent Disease	Without Tamoxifen	With Tamoxifen	*p* Value	Without Tamoxifen	With Tamoxifen	*p* Value
NSABP B-24[89]	1799	15-yr actuarial	DCIS	7.6	6.7	0.33	2.8	1.6	—
			Invasive	9.0	6.6	0.03	5.3	3.3	—
			DCIS + invasive	16.6	13.2	—	8.1	4.9	0.33
UKCCCR[91]	1576	12.7-yr median	DCIS	12.1	8.6	0.03	1.3	0.3	0.08
			Invasive	6.9	6.8	0.79	2.7	1.5	0.03
			DCIS + invasive	19.6	15.7	0.04	4.2	1.9	0.005

DCIS, *Ductal carcinoma in situ;* NSABP, *National Surgical Adjuvant Bowel and Breast Project;* UKCCR, *United Kingdom Coordinating Committee on Cancer Research;* yr, *year.*

TABLE 62-5 Prospective Studies Evaluating the Role of Excision Alone

	Years	Number of Patients	Follow-Up (months)	Local Recurrence Rate (Time Point)
NSABP B-17[89]	1985-1990	403	207	35.0 (15 years)
EORTC 10853[90]	1986-1996	503	188	31% (15 years)
Swedish DCIS[92]	1987-1999	520	240	Absolute difference 12% (20 years)
UKCCR[91]	1990-1998	508	151	19.4% (12 years)
RTOG 9804[114]	1999-2006	298	78	3.2% (5 years)
Dana Farber[113]	1995-2002	158	132	13% (8 years)
ECOG E-5194[115]	1997-2002	670	104	15.4%/15.1% (low grade/high grade, 10 years)
University of Southern California[109]	1996-2009	604	75	VNPI 4-6: 5.4% (12 years) VNPI 7: 30% (12 years)

DCIS, *Ductal carcinoma in situ;* ECOG, *Eastern Cooperative Oncology Group;* EORTC, *European Organisation for Research and Treatment of Cancer;* NSABP, *National Surgical Adjuvant Breast and Bowel Project;* RTOG, *Radiation Therapy Oncology Group;* UKCCR, *United Kingdom Coordinating Committee on Cancer Research.*

protocol B-17, designed to evaluate the role of postoperative irradiation.[84,89-91] All 814 evaluable patients enrolled were initially diagnosed with DCIS and underwent lumpectomy achieving clear surgical margins (i.e., inked specimen margins that were tumor free on histologic testing). Patients were subsequently randomized to receive postoperative whole-breast radiotherapy or no radiotherapy. The radiotherapy guidelines used consisted of whole-breast tangential fields treated to 50 Gy as per previous NSABP studies; a boost to the surgical bed was not included. With 15 years of follow-up, the rate of in-breast tumor recurrence with lumpectomy only was 35.0%, as compared with 19.8% when irradiation was delivered. Nine pathologic features were evaluated for their ability to predict for in-breast recurrence: comedo necrosis remained as a significant predictor for recurrence.[101]

A second randomized Phase III trial evaluating the role of radiotherapy after complete local excision was completed by the European Organization for Research and Treatment of Cancer (EORTC 10853) enrolling more than 1000 patients.[90,92] All patients had histologically confirmed tumor-free margins, defined as no DCIS at the inked margin, and the prescribed radiotherapy consisted of whole-breast tangential fields treated to 50 Gy in 25 fractions. A boost dose was not advised, and only 5% received a boost to the surgical bed. At a median follow-up interval of 15.8 years, researchers reported a 31% in-breast failure rate with excision only and an 18% in-breast failure rate with excision plus radiotherapy.[90] Risk factors for recurrence were evaluated, and the relative benefit from the addition of radiotherapy was equivalent in all subgroups. It should be noted that there were two groups identified with an exceptionally low risk of recurrence of less than 10%. These groups were defined as those with well-differentiated DCIS with either a clinging or micropapillary growth pattern. The relative benefit of radiotherapy remained consistent in these patient groups, but the absolute benefit was reduced.[90,102]

The United Kingdom Coordinating Committee on Cancer Research (UKCCCR) DCIS Working Group and investigators from Australia and New Zealand have also conducted a randomized trial investigating the role of adjuvant irradiation (Table 62-5).[91] Within a more complex 2 × 2 factorial protocol design, the aim was to compare four treatment regimens: excision alone, excision plus tamoxifen, excision plus radiotherapy, and excision plus radiotherapy and tamoxifen. Tamoxifen was prescribed as 20 mg/day, and radiotherapy was delivered through whole-breast tangential fields to a total dose of 50 Gy. A boost was not recommended. A total of 1030 patients were enrolled in the radiation arm of the trial. With a median follow-up of 12.7 years, radiation therapy was associated with a reduction in ipsilateral invasive (HR 0.32, $p < 0.0001$) and noninvasive recurrences (HR 0.38, $p < 0.0001$). The addition of tamoxifen to radiotherapy offered minimal benefit toward the overall ipsilateral local control rates; however, it did appear to reduce the ipsilateral recurrence rate of DCIS (HR 0.70, $p = 0.03$) and contralateral events (HR 0.44, $p = 0.005$).[91]

The SweDCIS study from the Swedish Breast Cancer Group enrolled 1067 patients from 1987 to 1999, randomizing between lumpectomy followed by radiotherapy and lumpectomy only for treatment of DCIS.[92] Patients underwent a sector resection with the aim of achieving a 1-cm gross surgical margin; microscopic clear resection was not required. The majority of

patients received 50 Gy in 25 fractions to a whole-breast treatment target. A split course of 54 Gy in 2-Gy fractions delivered in two treatment series separated by a 2-week break was allowed. No boost dose was delivered. A recent 20 year update found the absolute difference in local recurrence to be 12% with an absolute reduction of 10% for DCIS recurrences and 2% for invasive recurrences. Subgroup analysis by age, lesion size, focality, completeness of excision, and the presence of a lesion detected by screening confirmed that all groups benefited in risk reduction with the addition of radiotherapy.[92]

In a trial asking a similar question of the role of tamoxifen and building on the results from B-17, the NSABP initiated a trial to determine if the addition of tamoxifen to lumpectomy and postoperative radiotherapy would be more effective than lumpectomy and postoperative radiotherapy alone.[89] All of the 1799 women underwent excision and were randomized to whole-breast irradiation and placebo or whole-breast irradiation followed by tamoxifen. The postoperative radiotherapy was delivered with standard tangential fields to a total dose of 50 Gy. The placebo or tamoxifen (10 mg twice daily) was continued for 5 years. At 15 years, the in-breast failure rate following lumpectomy, radiotherapy, and placebo was 16.6%, and it was reduced to 13.2% when tamoxifen was added to lumpectomy and radiotherapy. The occurrence rate of cancer in the contralateral breast was also reduced with the addition of tamoxifen from 8.1% to 4.9%.[89]

Risk factor assessment has been performed with the goals of determining which patients are ideal for breast-conservation therapy, which patients would be better treated with mastectomy, and which patients could be successfully managed with lumpectomy only. Single-institution studies and randomized studies have identified factors that predict for an increased risk of recurrence. Tumor size, the presence of comedo necrosis, the nuclear grade, young patient age, and the margin status have all been identified as factors associated with a higher risk of in-breast recurrence.[88-92,95,102-107] However, the addition of radiation therapy reduces the risk of recurrence in all cases; only when diffuse disease, signified by mammographic appearance or the inability to achieve clear surgical margins, is encountered is mastectomy the preferred method of surgical management.[25] In the absence of these high-risk factors, the prevalent question is whether a less-comprehensive treatment approach (i.e., wide excision only or lumpectomy and hypofractionated/accelerated partial breast irradiation) is sufficient. Although failure pattern data and retrospective analysis exist to confirm the validity of these more directed treatment approaches, confirmation by an appropriately designed clinical trial is lacking.[26,108]

The Van Nuys Prognostic Index is a proposed method of identifying patients whose risk of in-breast failure following lumpectomy is so low that adjuvant radiotherapy would be of minimal benefit.[108,109] This scoring index is based on tumor grade, tumor size, patient age, and surgical margin width. Achieving a clear margin of more than 1 cm has been determined to be an important predictor of this index. It is important to note that this determination is characterized by a comprehensive, exhaustive pathologic evaluation assuring that a 1-cm clear surgical margin is achieved in all directions. The scoring index was developed and evaluated at a single institution through retrospective analysis and has yet to be consistently independently validated.[110-112]

In a prospective single-arm study at the Dana-Farber/Harvard Cancer Center evaluating wide excision alone, 158 patients with grade I or II DCIS lesions of 2.5 cm or less were treated with wide excision with final surgical margins of 1 cm or more without further treatment.[113] Treatment with tamoxifen was not permitted. Presently accepted standard practice approaches to surgical resection and pathologic assessment were applied. The median follow-up time was 40 months. Accrual was prematurely closed after 13 patients developed local recurrence at an unacceptably high in-breast failure rate corresponding to a 5-year rate of 12%.[113]

The Radiation Therapy Oncology Group (RTOG) initiated a prospective randomized trial evaluating the need for radiotherapy in patients with low-risk DCIS. Following lumpectomy with clear margins of resection of 3 mm or more, patients were stratified according to age (<50 years versus ≥50 years), tumor size (≤1 cm versus >1 cm to 2.5 cm), margin status (negative reexcision versus 3 mm to 9 mm versus ≥10 mm), grade, and use of tamoxifen (at the discretion of the managing physician). After stratification, patients were randomized to whole-breast irradiation versus observation. This trial had a target accrual of 1800 patients but closed because of slow enrollment with 636 patients. At 5 years, the addition of radiation therapy significantly reduced local recurrence rates (0.4% versus 3.2%). Importantly, a patterns of failure analysis found that two thirds of recurrences in the observation-alone arm were true recurrences (in the same quadrant as the initial tumor), whereas none of the recurrences in the RT arm were true recurrences.[114]

In an intergroup trial run by the Eastern Cooperative Oncology Group (ECOG) and North Central Cancer Treatment Group, wide excision only in a population of conservatively selected patients with DCIS was evaluated.[104] Eligible patients included those with low- or intermediate-grade DCIS lesions measuring 2.5 cm or less or high-grade DCIS lesions measuring 1 cm or less. The microscopic margin width was required to be 3 mm or more with no residual calcifications on postoperative mammograms and 30% received tamoxifen. Six hundred and seventy patients were evaluable, and at 5/10 years, the rates of local recurrence were 6.1%/15.4% and 15.3%/15.1%, for the low- and intermediate-grade and high-grade cohorts, respectively.[115]

Alternatives to traditional whole-breast irradiation have emerged as modalities to shorten the duration of adjuvant radiation therapy. Accelerated partial breast irradiation allows for the delivery of treatment in 1 week or less. While waiting for results from NSABP B-39, multiple studies have emerged demonstrating low rates of local recurrence and excellent toxicity profiles in patients with DCIS.[116-118] Evidence-based guidelines allow for the use of partial-breast irradiation in patients with DCIS at this time off-protocol.[116-118] With regard to hypofractionation, increasing data has demonstrated equivalent efficacy to whole-breast irradiation though data is limited in the setting of DCIS.[119-121]

Recently, there has been renewed interest in identifying those patients with DCIS who may not benefit from adjuvant radiation therapy. Although previous approaches and trials used clinical and pathologic criteria, more recently data has emerged on the role of multigene assays in patients with DCIS. Solin et al evaluated 327 patients from the ECOG trial with adequate tissue for multigene assay using three risk categories: low (DCIS score <39), intermediate (39-54), and high risk (≥55). DCIS score, as a continuous variable, was found to be significantly associated with ipsilateral breast tumor recurrence after adjusting for tamoxifen utilization; on multivariate analysis, DCIS score remained significantly associated. By risk group, the 10-year rate of IBTR was 10.6%, 26.7%, and 25.9% for low, intermediate, and high-risk groups, respectively, and for invasive IBTR the rates were 3.7%, 12.3%, and 19.2%, respectively.[115] Further prospective study is required, although these data do suggest the possibility of tumor genetics identifying patients at low risk suitable for treatment with lumpectomy alone. However, there still remain concerns as the low-risk cohort still had a greater than 10% risk of recurrence.

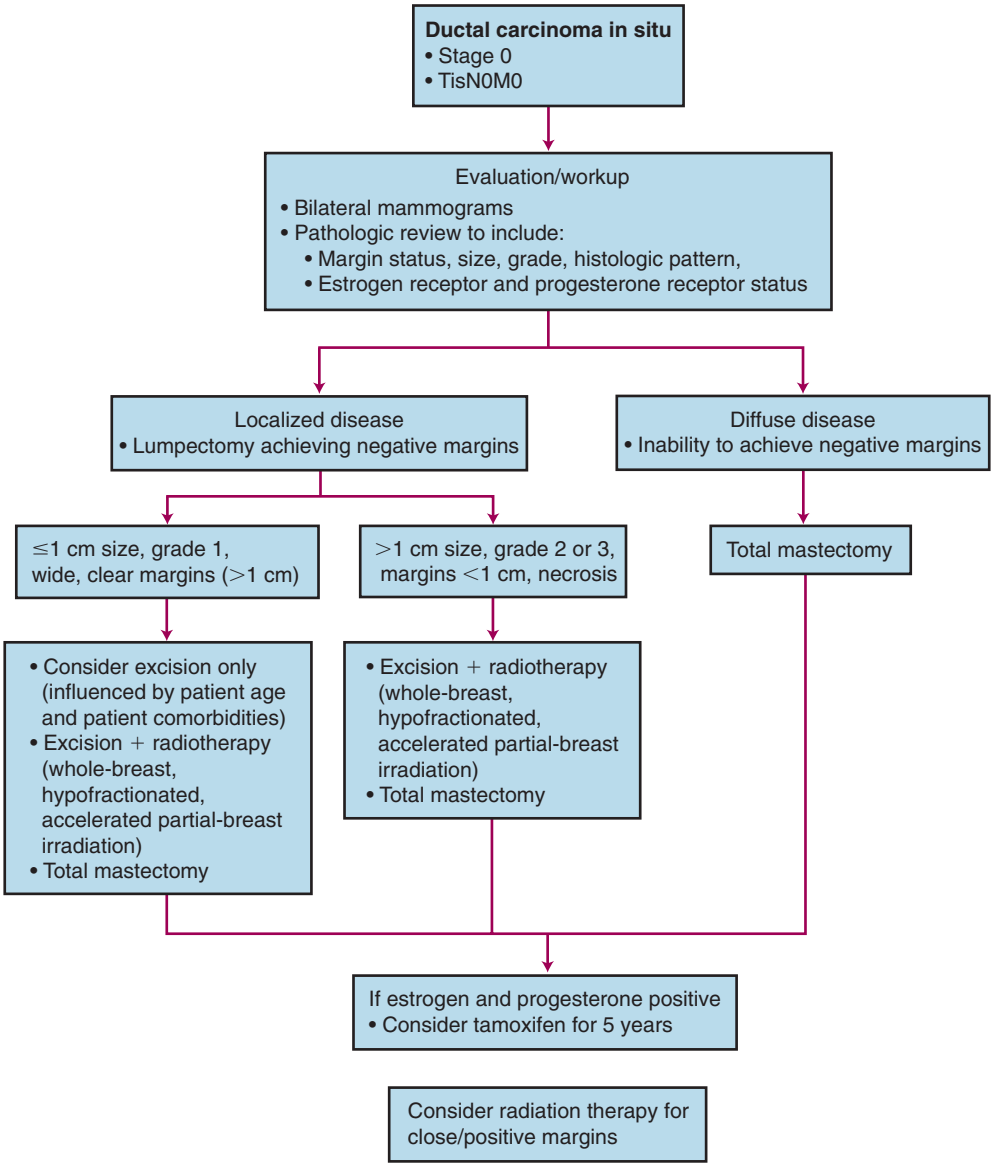

Figure 62-3 Management decision tree for ductal carcinoma in situ.

In summary, DCIS is a noninvasive malignant tumor that is managed successfully with treatment directed toward the breast only (Figure 62-3). Treatment approaches addressing the whole breast are considered the standard of care, although hypofractionated and partial-breast treatment (i.e., wide excision only versus lumpectomy plus partial-breast irradiation) techniques are being evaluated. Although mastectomy can always be considered a treatment option, breast-conservation therapy is the preferred treatment approach. When considering a patient for standard breast-conservation therapy, it is important to first ensure that clinical and mammographic information confirms that the lesion is unicentric. When surgical excision of the lesion is performed, negative pathologic margins should be established and an acceptable cosmetic result achieved. Postoperative irradiation should be delivered with whole-breast tangential fields to a homogeneous dose of 46 Gy to 50 Gy in 1.8 Gy to 2 Gy per fraction. An additional dose to the surgical bed plus the tumor margin (1 cm to 2 cm) typically follows, so that the total cumulative dose to the surgical bed is 60 Gy to 66 Gy.

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