Ductal carcinoma in situ: Treatment and prognosis

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INTRODUCTION

Carcinoma in situ of the breast represents a heterogeneous group of neoplastic lesions confined to the breast ducts and lobules (ductal carcinoma in situ [DCIS]). The diagnosis of DCIS increased dramatically following the introduction of screening mammography and now comprises approximately 25 percent of all newly diagnosed breast cancers. The goal of therapy for DCIS is to prevent the development of invasive breast cancer. Therapeutic approaches include surgery, radiation therapy, and adjuvant endocrine therapy.

The treatment of DCIS will be reviewed here. The pathology, epidemiology, and diagnosis of DCIS and microinvasive carcinoma of the breast are presented separately.

- (See "Pathology of breast cancer".)
- (See "Breast ductal carcinoma in situ: Epidemiology, clinical manifestations, and diagnosis".)
- (See "Microinvasive breast carcinoma".)

TREATMENT APPROACH

Patients with DCIS undergo local treatment with breast-conserving therapy (BCT) or mastectomy. BCT consists of lumpectomy (also called breast-conserving surgery, wide excision, or partial mastectomy) followed in most cases by adjuvant radiation. Radiation therapy may be reasonably omitted in a select population of patients with low-risk disease. (See 'Local treatment' below and 'Omission of RT for low-risk disease' below.)

A sentinel lymph node biopsy (SLNB) can be avoided in most women. However, it should be obtained in women with high-risk features for whom resection (mastectomy or BCT) may compromise the ability to perform a future SLNB. (See 'Indications for SLNB' below.)

BCT is generally preferred as the local treatment, although mastectomy may be an option in some cases. The decision to administer endocrine therapy to reduce the risk of subsequent cancers depends upon the choice of local therapy and the tumor hormone receptor status (see 'Endocrine therapy' below):

- BCT; estrogen/progesterone receptor (ER/PR) positive – We offer five years of endocrine therapy for treatment and risk reduction, with choice of therapy dependent on the patient's menopausal status. Tamoxifen is used for premenopausal women. For postmenopausal women, either tamoxifen or aromatase inhibitors are acceptable options.

- Mastectomy; ER/PR positive – In such cases, consider endocrine therapy for prevention of contralateral breast cancer.

- BCT or unilateral mastectomy; ER/PR negative – While the benefit is less clear and we do not routinely utilize endocrine therapy in this setting, some women may prefer to take adjuvant tamoxifen to prevent the low risk of a new ER-/PR-positive contralateral or ipsilateral breast cancer.

- Bilateral mastectomy – For women who have undergone bilateral mastectomy, there is no role for adjuvant endocrine therapy.

Post-treatment surveillance consists of regular history and physical examination and mammography (if applicable), without routine utilization of laboratory tests, tumor markers, or other imaging. (See 'Post-treatment surveillance' below.)

LOCAL TREATMENT

DCIS of the breast represents a broad biologic spectrum of disease. The best form of local therapy is debated.

Local treatment for DCIS usually involves breast-conserving therapy (BCT), which consists of lumpectomy (also called wide excision or partial mastectomy) followed in most cases by adjuvant radiation therapy (RT). Alternatively, mastectomy may be considered. In some instances, sentinel lymph node biopsy (SLNB) may also be performed.

Mastectomy versus BCT — Both mastectomy and breast-conserving therapy (BCT) are reasonable options for most women with DCIS, although not all women will meet the criteria for BCT. A choice between these is a personal one and should be made after discussion

between patient and provider (see 'Criteria for BCT' below). BCT generally affords a better quality of life than mastectomy with reconstruction [1].

Patients found to have invasive or microinvasive disease at surgery should be managed accordingly. (See "Overview of the treatment of newly diagnosed, invasive, non-metastatic breast cancer" and "Microinvasive breast carcinoma".)

Relative efficacy — Although mastectomy achieves excellent long-term survival with a local recurrence rate on the order of 1 percent, it provides overly aggressive treatment for many women. BCT has less morbidity but is associated with a higher risk of local recurrence [2-9].

In a 2015 observational study that included over 100,000 patients who received a diagnosis of DCIS in the Surveillance, Epidemiology, and End Results (SEER) database, when compared with lumpectomy (with or without radiotherapy), mastectomy resulted in a similar 10-year breast cancer-specific mortality (multivariate hazard ratio [HR] for mastectomy versus lumpectomy 1.2, 95% CI 0.96-1.50) [3]. While this study did not report on morbidity associated with each surgery, information regarding the relative safety of each surgery comes from data of early breast cancer, which suggest that while postoperative complication rates associated with either surgery are low, they are more frequent with mastectomy [10]. Postoperative morbidities associated with mastectomy and BCT are discussed in more detail separately. (See "Mastectomy", section on 'Complications' and "Breast-conserving therapy", section on 'Complications'.)

Together these data suggest that BCT for DCIS offers a low rate of recurrence with minimal complications. However, mastectomy is a reasonable alternative for women who wish to take all possible measures to minimize risk of recurrence and/or avoid radiation (if applicable).

Criteria for BCT — Women with DCIS are candidates for breast-conserving therapy (BCT) as long as the following criteria are met:

- Multifocal disease (ie, two or more foci contained within a limited area and usually the same quadrant of the breast) is not necessarily a contraindication to BCT [11]. Multicentric disease (ie, two or more foci separated by significant distance and usually involving more than one quadrant) is a relative contraindication.

- Cosmetically acceptable resection is achievable given the size of disease relative to size of the breast.

- Histologically negative margins can be achieved with lumpectomy. Negative margins are defined by tumor-filled ducts separated by a measurable distance from the inked surface (ie, 2 mm). It is recognized that it may not be possible to obtain these margin widths, particularly with DCIS close to the skin or muscle [12]. If the area of concern is

close to the fascia, the dissection should be carried down to and include resection of the pectoral fascia [13-15]. (See 'Margin width' below.)

Patients whose disease does not fit the above criteria should proceed with mastectomy.

Mastectomy

Efficacy — Mastectomy is curative for over 98 percent of patients with DCIS [16-20]. Disease recurrence is rare after mastectomy (1 to 2 percent) [4,21-23]. Postmastectomy recurrences may be the result of unrecognized invasive carcinoma, inadequate margins, or incomplete removal of breast tissue at the time of mastectomy. (See 'Margin width' below.)

Women treated with mastectomy are candidates for breast reconstruction; immediate reconstruction is usually preferred if the woman is eligible. (See "Overview of breast reconstruction".)

Patients undergoing mastectomy for DCIS may benefit from SLNB. (See 'Indications for SLNB' below.)

Women with unilateral DCIS are at a modestly increased risk of developing either invasive breast cancer or DCIS in the contralateral breast, approximately 1 percent for every year of life (and higher for genetic reasons) [4,21]. Therefore, some women with DCIS choose contralateral prophylactic mastectomy to prevent a future breast cancer in the contralateral breast [22] despite a lack of a proven survival benefit. Alternatively, women who have undergone unilateral mastectomy for DCIS may elect endocrine therapy as chemoprevention against a future primary breast cancer in the contralateral breast. For women who have undergone bilateral mastectomy, there is no role for adjuvant endocrine therapy. (See "Contralateral prophylactic mastectomy" and 'Endocrine therapy' below.)

Postmastectomy RT is **not** routinely indicated for DCIS but may be considered on a case-by-case basis if an extensively positive margin is discovered upon pathologic review of the surgical specimen. (See 'Margin width' below.)

Indications for SLNB — While sentinel lymph node biopsy (SLNB) is not indicated for most patients with DCIS, SLNB can be considered for women requiring mastectomy for DCIS. (See 'Criteria for BCT' above.)

After a total mastectomy, the lymphatic drainage pattern will be permanently altered, making it impossible to accurately perform SLNB at a later date if invasive cancer is found unexpectedly in the mastectomy specimen. Patients who require a mastectomy have a higher likelihood of harboring an invasive cancer compared with women with a smaller focus of disease and therefore should undergo an SLNB at the time of surgery [24].

By contrast, our practice is not routinely to pursue SLNB in patients who are candidates for BCT yet opt for mastectomy, given that the likelihood of invasive cancer in such patients is low. We recognize, however, that practice patterns vary, and others may reasonably choose to perform SLNB routinely for all patients undergoing mastectomy for DCIS.

Breast-conserving therapy — BCT for DCIS refers to lumpectomy to remove the tumor with negative surgical margins, generally followed by RT to eradicate any occult residual disease [2,4-9,11,13-15].

Surgical resection — The goal of BCT for DCIS is complete resection with negative margins in a cosmetically acceptable manner. When DCIS is present on a core biopsy, needle, wire, reflector, or seed localization under image guidance prior to surgical excision may ensure complete resection. For larger areas of suspicious microcalcifications, bracketing of the area maximizes the likelihood of a complete excision with adequate margins on the first attempt, thereby diminishing the need for re-excision [25,26].

For patients whose disease is associated with suspicious calcifications on preoperative mammography or in whom the adequacy of the margins is in question, a postexcision mammogram should be obtained prior to initiation of radiation. Residual suspicious calcifications warrant an image-guided (wire, reflector, tracer) approach to re-excision [27-29]. (See 'Margin width' below and "Diagnostic evaluation of suspected breast cancer", section on 'Mammographic features of breast cancer'.)

In an observational cohort study of 140,366 patients with DCIS in the SEER database, the 15-year breast cancer mortality rate was 1.7 percent for those treated with lumpectomy and radiation versus 2.3 percent for patients treated either with lumpectomy alone (HR 0.77, 95% CI 0.67-0.88) or with mastectomy (HR 0.75, 95% CI 0.65-0.87), suggesting that BCT is at least equivalent, if not better, than mastectomy in this setting [30]. Further discussion of the contributions of radiation after lumpectomy, and omission for certain patients, is found below. (See 'Benefits of treatment' below and 'Omission of RT for low-risk disease' below.)

SLNB not routinely indicated with BCT — Sentinel lymph node biopsy (SLNB) is not indicated for most patients undergoing breast-conserving therapy (BCT) for DCIS. Omitting SLNB at the time of breast-conserving surgery for DCIS decreases perioperative morbidity [31-33]. Because DCIS is a preinvasive lesion, axillary nodes are rarely positive in DCIS, even in cases of extensive multifocal high-grade disease [24,34-40]. In one retrospective review, none of 297 patients with a final diagnosis of DCIS had a positive SLNB [37].

If invasive breast cancer is identified after a breast-conserving surgery is performed for DCIS, SLNB can be performed as a second procedure. Upstaging to invasive carcinoma has been reported in 10 to 20 percent of excision specimens following a core biopsy diagnosis of DCIS [41]. Disease stage and subsequent axillary management may change for such patients

based on the new stage of the breast cancer [32,33]. (See "Tumor, node, metastasis (TNM) staging classification for breast cancer" and "Microinvasive breast carcinoma" and "Overview of the treatment of newly diagnosed, invasive, non-metastatic breast cancer".)

Radiation therapy — RT is the standard for patients treated with BCT, though it may be reasonable to omit in selected patients with advanced age, extensive comorbidities, or small foci of low-grade disease resected with wide negative margins. (See 'Omission of RT for low-risk disease' below.)

RT after lumpectomy reduces the risk of local invasive and noninvasive recurrences. As described below, randomized trials have shown that adjuvant RT significantly reduces the risk of in-breast tumor recurrence by 50 percent or greater compared with excision alone. However, treating all women who undergo breast-conserving surgery for DCIS with adjuvant RT may be overtreatment for some [42,43]. The majority of cases of DCIS do not recur when treated with excision alone, and there may be subgroups of patients with DCIS in whom the risk of local recurrence is so low that RT may be of no benefit. The difficulty, however, is in reliably predicting those patients who would not recur in the absence of RT. (See 'Omission of RT for low-risk disease' below.)

Benefits of treatment — RT significantly reduces the odds of in-breast recurrence but likely does not change the odds of distant recurrence or mortality, and therefore it should be discussed with each patient carefully.

The benefit of RT for DCIS was shown in a 2009 meta-analysis of RT compared with no further treatment following lumpectomy [44]. Compared with lumpectomy alone, RT resulted in a reduction in the risk of all ipsilateral breast events (pooled HR 0.49, 95% CI 0.41-0.58). This translated into a number needed to treat of nine women to prevent one ipsilateral breast recurrence.

In addition, the risk reduction for local recurrence associated with RT appears to be long-lasting, though this is not associated with a survival advantage. This was shown in a report of the long-term follow-up of the National Surgical Breast and Bowel Project (NSABP) B-17 trial [8]. At 15 years, compared with excision alone, RT resulted in:

- A lower rate of ipsilateral invasive recurrence (8.9 versus 19.4 percent)
- Similar overall survival (83 versus 84 percent) and cumulative all-cause mortality rate through 15 years (HR for death 1.08, 95% CI 0.79-1.48, 17.1 versus 15.8 percent)

Similar findings were reported from a large 2015 observational study of the SEER database that included over 100,000 patients with DCIS [3] and a 2021 cohort study from the Netherlands [45]. Other observational data have suggested a survival benefit, particularly for patients with high-risk disease [30,46]. (See 'Surgical resection' above.)

RT schedule — As in the treatment of invasive breast cancer, the standard of care for patients undergoing BCT is to deliver adjuvant whole-breast radiation therapy (WBRT), typically within eight weeks of surgery. Conventionally dosed WBRT consists of 1.8 to 2 Gy daily fractions over 4.5 to 5 weeks to a total dose of 45 to 50 Gy, often followed by a boost to the surgical bed. Hypofractionated RT has gained acceptance for pure DCIS. Patient selection for hypofractionation is discussed elsewhere. (See "Adjuvant radiation therapy for women with newly diagnosed, non-metastatic breast cancer", section on 'Conventional versus hypofractionated schedules'.)

- **RT Schedule –** Data regarding RT schedule among patients with DCIS are as follows:
  - For women who will undergo adjuvant RT as a component of BCT, an observational study in 1323 women with a median follow-up of 6.6 years suggested that earlier initiation of RT (ie, ≤8 weeks) was associated with a lower incidence of ipsilateral breast tumor recurrence than among patients with later initiation of RT (ie, >12 weeks) [47]. (See "Adjuvant radiation therapy for women with newly diagnosed, non-metastatic breast cancer".)
  - Rapid-fractionation schedules or accelerated partial-breast RT are under investigation and early results are promising [48-51]. In two single-institution trials that enrolled a total of 145 women who had undergone breast-conserving surgery for DCIS, patients received accelerated partial-breast RT (41 to 42 Gy delivered over 15 fractions) [49]. In a combined analysis, the recurrence rate at five years was 4 percent, which was similar to the rate of recurrence following WBRT reported in the NSABP B-17 trial (range, 3 to 8 percent for noninvasive and invasive recurrences, respectively) [52]. Hypofractionation in DCIS was evaluated in the BIG 3-07/TROG 07.01 study [53]. Patients were randomly assigned to a tumor bed boost and/or hypofractionated whole breast RT in a 1:1:1:1 allocation. At a median follow-up of 6.6 years, there was no statistically significant difference in five-year freedom from disease recurrence between the hypofractionated and conventionally fractionated arms. Some trials included patients with either early breast cancer or DCIS, and are discussed elsewhere. (See "Adjuvant radiation therapy for women with newly diagnosed, non-metastatic breast cancer", section on 'Conventional versus hypofractionated schedules'.)
- **Use of a boost –** Use of a boost to the surgical bed in DCIS is discussed elsewhere. (See "Adjuvant radiation therapy for women with newly diagnosed, non-metastatic breast cancer", section on 'RT boost to the tumor bed'.)

Omission of RT for low-risk disease — As described above, radiation therapy (RT) reduces the odds of in-breast recurrence but likely does not change the odds of distant recurrence or decrease mortality. For patients with low-risk disease that has been fully resected with widely

negative margins, and particularly if it is ER-positive and endocrine therapy will be administered, the absolute reduction of in-breast recurrence may not be large enough to justify the risks associated with RT [54]. In such patients, it is reasonable to omit RT, especially in the setting of comorbidity, advanced age, or patient preference. We are less likely to omit radiation for young women, however, given some data suggesting RT is more likely to benefit these patients [46].

While the results from the NSABP B-17 trial described above have been used to argue for RT in all women who undergo lumpectomy for pure DCIS, methodologic issues such as suboptimal pathologic evaluation and uncertainty about the completeness of excision may have led to an overestimation of the benefit of RT in this study. Moreover, RT is expensive, time consuming, and may be accompanied by significant side effects, and so omission for patients likely to derive the least benefit is reasonable. (See "Radiation therapy techniques for newly diagnosed, non-metastatic breast cancer".)

Since RT reduces the risk of ipsilateral recurrence without changing the risk of developing contralateral disease, omission of RT would be a reasonable approach for patients with an ipsilateral recurrence risk approximately equal to the risk of developing contralateral disease. Among women diagnosed with DCIS, the long-term risk of developing a contralateral breast cancer or DCIS is approximately 3 to 10 percent [55-57]. As described below, studies have tried to identify such a low-risk population using histopathologic and gene expression analysis. While it is difficult to identify a clear-cut low-risk population, the benefit of RT becomes less clear as the risk of ipsilateral recurrence approaches that of contralateral recurrence.

Histopathologic criteria — While there are no strict criteria for "low risk," our approach has been to define low risk as DCIS that is low- or intermediate-grade, small (<2.5 cm in size), and resected with widely negative margins (≥1 cm). (This negative margin cutoff is more conservative than that used in the studies described below). Omission of RT in such patients is reasonable, although associated with a small risk of ipsilateral recurrence.

Several studies suggest that clinical pathologic criteria may define a low-risk cohort of patients with DCIS for whom RT may be reasonably omitted given a low risk of recurrence. These studies are summarized below.

The Eastern Cooperative Oncology Group (E5194) was an observational study that investigated excision without RT in women with low- to intermediate-grade versus high-grade DCIS [58,59]. Eligible patients had <2.5 cm of low- to intermediate-grade DCIS or <1.0 cm for high-grade DCIS. Margins ≥3 mm were required and a negative postexcision mammogram was obtained for all participants. Tamoxifen following excision was allowed but not mandated. With a median follow-up of 6.7 years, the following local recurrent rates (LRR) were reported:

- Five-year LRR for low- or intermediate-grade DCIS (n = 565) was 6.1 percent (95% CI 4.1-8.2).
- Five-year LRR for high-grade DCIS (n = 105) was 15.3 percent (95% CI 8.2-22.5).
- The 12-year LRRs for the low- or intermediate-grade group versus the high-grade group were 14.4 and 24.6 percent, respectively.

These results suggest that patients with low- to intermediate-grade DCIS may be better candidates for local excision alone than those with high-grade lesions who have a higher risk of recurrence. However, a 10-year LRR approaching 15 percent in patients with low- or intermediate-grade DCIS may not be low enough to justify the routine omission of postexcision RT even in this patient population. This 10-year rate of LRR occurred despite a median tumor size of only 6 mm.

The Radiation Therapy Oncology Group 9804 trial, which was closed early due to low accrual, investigated outcomes of RT omission in the setting of low-risk DCIS, randomizing 636 patients with low-risk disease to either RT or observation after surgery [60]. In this study, low risk consisted of low- or intermediate-grade DCIS measuring <2.5 cm with resection to negative margins of ≥3 mm. Median tumor size was 5 mm. While recurrence rates were decreased with RT, the recurrence rate was also low in the control group. With a median follow-up of seven years, RT resulted in:

- A reduced risk of a local recurrence compared with observation (0.9 versus 6.7 percent; HR 0.11, 95% CI 0.03-0.47).
- A higher rate of mild to moderate (grade 1 or 2) toxicities (76 versus 30 percent), although the rate of serious toxicities was similar in both arms (4 percent). Of patients treated with RT, grade 1, 2, or 3 late toxicities were seen in 30, 5, and 0.7 percent, respectively.
- No difference in either disease-free survival or overall survival.

  Results at longer follow-up also showed lower local recurrence rates with RT (15-year ipsilateral breast recurrence rates of 7.1 versus 15.1 percent without versus with RT, respectively; HR 0.36, 95% CI 0.20-0.66) [61].

Identifying patients who can safely be managed with surgical excision alone using clinicopathologic data remains a challenge, and some patients may value the reduction in recurrence (DCIS and invasive) enough to warrant pursuing postexcision RT regardless of their risk factors.

Gene expression analysis — Gene expression analysis such as the Oncotype DX DCIS recurrence score and DCISionRT have been studied as a tool for identification of patients for

whom postlumpectomy RT may reasonably be omitted [62-65], but data regarding its utility are still limited. Further validation of these results is required before the multigene assay can become a standard part of clinical practice [66].

Although gene expression analyses in DCIS patients are not routine, if a DCIS recurrence score has already been obtained, it should be considered within the context of known prognostic factors (ie, tumor size, grade, and margin width) as well as radiation-related factors (ie, cost, convenience, and possible side effects) in consideration for omission of RT after lumpectomy.

Pathologic examination — For patients with DCIS, complete tissue processing is important to exclude small foci of invasive carcinoma, determine the size and/or extent of DCIS, ascertain the presence of contiguous or multifocal distribution, and evaluate the distance to the resection margins (margin width) [67-69]. However, for large specimens this may not be practical, and in such cases we focus on complete examination of the fibrous parenchyma (omitting the fatty tissue).

Key pathologic components — The pathology report should include the following:

- Nuclear grade and necrosis (ie, low, intermediate, or high; presence or absence of comedo necrosis).
- The size or extent of the lesion.
- The distance to the closest margin, including whether the margins were only focally or extensively involved [70,71].
- Specimen orientation by the surgeon to identify specific margins and allow for targeted re-excision if necessary.
- Estrogen receptor expression. This result guides systemic therapy decisions [72,73]. (See 'Systemic treatment' below.)

The role of human epidermal growth factor receptor 2 (HER2) expression in DCIS is evolving. However, at present, consensus guidelines do not recommend routine testing of pure DCIS for HER2 overexpression [72,74]. (See "HER2 and predicting response to therapy in breast cancer", section on 'Clinical utility of HER2 testing'.)

The pathology of DCIS is discussed separately. (See "Pathology of breast cancer".)

Margin width — The margin width (distance between the edge of the DCIS and the inked margins) reflects the completeness of excision and is an important determinant of local recurrence in DCIS, particularly for patients considering foregoing radiotherapy after breast-

conserving surgery. Preferred margin width for DCIS is discussed elsewhere. (See "Breast-conserving therapy", section on 'Margins for DCIS'.)

SYSTEMIC TREATMENT

The primary role of systemic treatment is to reduce the risk of invasive breast cancer in the ipsilateral and/or contralateral breast. Chemotherapy plays no role in the management of these patients given the low risk of distant metastatic disease and overall good prognosis.

Endocrine therapy is offered to the majority of patients with hormone receptor-positive DCIS. (See 'Indications' below.)

There is no current indication for human epidermal growth factor receptor 2 (HER2)-directed therapy in the management of DCIS. (See 'Is there a role for HER2-directed therapy?' below.)

Endocrine therapy — Approximately 75 percent of DCIS lesions express estrogen receptors (ER) and/or progesterone receptors (PR) [75-77]. Of the endocrine agents approved for use as adjuvant therapy for invasive breast cancer, only tamoxifen is approved in the United States to prevent invasive breast cancer recurrences in women with DCIS, although data reviewed below indicate that the aromatase inhibitor anastrozole is also an acceptable option. (See 'Aromatase inhibitors' below.)

Indications — Following local treatment, the decision to administer endocrine therapy to reduce the risk of subsequent cancers depends upon the tumor hormone receptor status and the choice of local therapy. While testing of DCIS for ER is recommended to determine potential benefit of endocrine therapies to reduce risk of future breast cancer, testing of DCIS for PR is considered optional [78]. Further discussion of the interpretation of hormone receptor expression in breast cancer is found elsewhere. (See "Hormone receptors in breast cancer: Clinical utility and guideline recommendations to improve test accuracy", section on 'Analysis of ER and PR expression'.)

Our approach is as follows:

- For women with ER-positive DCIS who have **not** undergone a bilateral mastectomy, we suggest endocrine therapy rather than observation, and both tamoxifen and the aromatase inhibitor anastrozole are reasonable. Endocrine therapy reduces recurrence rates, but has not been shown to improve survival. The data to support this recommendation are discussed below. (See 'Tamoxifen' below and 'Aromatase inhibitors' below.)

- We do not routinely utilize tamoxifen as chemoprevention for women with ER-negative DCIS given that the benefit of endocrine therapy does not reduce the risk of recurrence

in this population. Some women may opt to take tamoxifen, however, to decrease the risk of developing a new endocrine receptor-positive DCIS or breast cancer. (See 'Tamoxifen' below.)

- In women having bilateral mastectomies for DCIS, the risks of adverse effects from tamoxifen outweigh any potential benefit for risk reduction.

Tamoxifen

Efficacy — For women with ER-positive DCIS treated with breast-conserving therapy (BCT), we offer postoperative tamoxifen treatment for five years to prevent ipsilateral recurrences and new events, both in the ipsilateral and contralateral breast. The risks of side effects, including endometrial cancer and thromboembolic events, while small, need to be discussed with the patient. (See "Managing the side effects of tamoxifen and aromatase inhibitors".)

For women treated with BCT, multiple trials have demonstrated that postoperative tamoxifen is more effective than placebo in reducing the risk of invasive breast cancer, with or without adjuvant radiotherapy, although there is no apparent benefit for survival [8,55,79,80]. This was illustrated in a meta-analysis of two randomized trials, National Surgical Adjuvant Breast and Bowel Project (NSABP) B-24 and United Kingdom, Australia, and New Zealand DCIS, which together included 3375 patients [81]:

- The addition of tamoxifen to BCT for DCIS reduced the recurrence risk of ipsilateral DCIS (hazard ratio [HR] 0.75, 95% CI 0.61-0.92) and contralateral DCIS (relative risk [RR] 0.50, 95% CI 0.28-0.87). The patients receiving tamoxifen had a 10-year rate of 5.6 percent for noninvasive breast cancers in the ipsilateral breast compared with 7.2 percent for those treated with placebo.

- There was a trend towards a lower risk of ipsilateral invasive carcinoma (HR 0.79, 95% CI 0.61-1.01) that did not reach statistical significance and a lower risk for contralateral invasive carcinoma (RR 0.57, 95% CI 0.39-0.83). The patients receiving tamoxifen had a 10-year rate of 4.6 percent for invasive cancers versus 7.3 percent among those receiving placebo.

- There was no benefit of tamoxifen in all-cause mortality (RR 1.11, 95% CI 0.89-1.39).

The benefit of postoperative tamoxifen is primarily in patients with ER-positive DCIS. The ability of ER status to predict response to tamoxifen for women with DCIS was addressed in a retrospective review of data from the NSABP B-24 trial that included 41 percent of the original cohort (732 patients) [56]. At 10 years of follow-up, patients with ER-positive DCIS treated with tamoxifen had significant decreases in any subsequent (invasive and/or noninvasive; ipsilateral and/or contralateral) breast cancer events compared with patients

receiving placebo (HR 0.58, 95% CI 0.42-0.81). No significant benefit was observed in ER-negative DCIS.

Dose — When using tamoxifen for DCIS, we administer it at the standard dose of 20 mg orally daily, which was the dose evaluated in the clinical trials discussed above. However, for women with DCIS who would otherwise discontinue endocrine therapy due to substantial toxicities, we offer lower-dose tamoxifen (10 mg every other day) rather than ending treatment. In such instances, we discuss that efficacy data supporting lower-dose tamoxifen are limited to a single trial that did not compare it with standard dose treatment.

In a trial of 500 patients who had been treated with lumpectomy for atypical ductal hyperplasia, lobular carcinoma in situ (LCIS), or ER-positive or unknown DCIS (with radiation for high-risk features), the rate of recurrence of either intraepithelial neoplasia or invasive breast cancer was 5.7 percent among those receiving tamoxifen 5 mg daily versus 11.9 percent for those receiving placebo (HR 0.48, 95% CI 0.25-0.89) at a median follow up of 5.1 years [82]. Benefits were maintained at longer follow-up (almost 10 years) [83]. Approximately 70 percent of patients in the trial had DCIS. There were 8 serious adverse events in the tamoxifen arm and 12 in the placebo arm. The relative risk reduction with tamoxifen in this trial is similar to that in trials that used a higher dose of tamoxifen, but the rate of severe toxicity relative to placebo is less. However, a limitation of this trial was that treatment adherence was only about 60 percent in either arm.

A subsequent trial evaluating side effects of varying doses of tamoxifen found that low versus standard dose tamoxifen was associated with less pronounced side effects in premenopausal women [84].

Aromatase inhibitors — The aromatase inhibitor anastrozole is a reasonable alternative to tamoxifen in postmenopausal women with ER-positive DCIS. Toxicities associated with aromatase inhibitors include loss of bone density, fractures, and cardiovascular risk and should be discussed with the patient. Side effects of aromatase inhibition is discussed in detail elsewhere. (See "Adjuvant endocrine and targeted therapy for postmenopausal women with hormone receptor-positive breast cancer", section on 'Side effects' and "Evaluation and management of aromatase inhibitor-induced bone loss".)

The NRG Oncology/NSABP B-35 trial, which enrolled over 3100 postmenopausal women with hormone receptor-positive DCIS who underwent BCT, demonstrated that anastrozole resulted in a decreased rate of breast cancer events at 10 years compared with tamoxifen [85]. Patients were randomly assigned to treatment with tamoxifen or anastrozole for five years. At a median follow-up of nine years, when compared with tamoxifen, anastrozole resulted in:

- A lower incidence of subsequent breast cancer events (ie, recurrent DCIS or subsequent invasive breast cancer) (90 versus 122 events, respectively; HR 0.73), including a lower rate of invasive breast cancer (43 versus 69 cases; HR 0.62).
- Improved estimated breast cancer-free survival at 10 years (93.1 versus 89.1 percent).
- No significant difference in either disease-free survival (235 versus 260 events; HR 0.89, 95% CI 0.75-1.07) or overall survival (OS; 98 versus 88 deaths; HR 1.11, 95% CI 0.83-1.48). The estimated 10-year OS was approximately 92 percent for both groups.

The analysis also suggested that these benefits of anastrozole were mostly seen in women under age 60 years. These results support the use of anastrozole in postmenopausal women with DCIS. However, this study also confirms the overall good prognosis for women with DCIS. Therefore, decisions on whether anastrozole is indicated should be individualized based on the patient and her tumor characteristics.

Is there a role for HER2-directed therapy? — Current data are not sufficient to support use of human epidermal growth factor receptor 2 (HER2)-directed therapy in DCIS. We do not recommend HER2 testing of DCIS, in concordance with American Society of Clinical Oncology/College of American Pathologists guidelines [86].

Compared with invasive breast cancer, DCIS more often expresses HER2. As an example, in a study of 708 malignant ductal lesions (59 with DCIS, 649 with invasive disease), the proportion that were HER2-positive was 56 and 15 percent, respectively [87].

However, HER2 overexpression does not affect the management strategy of DCIS. Limited data demonstrate an immunologic response to a single dose of trastuzumab in patients with HER2-positive DCIS, though changes in other histologic markers were not noted [88].

POST-TREATMENT SURVEILLANCE

The goals of surveillance after treatment for DCIS are early recognition and treatment of potentially curable disease recurrences and second primary breast cancers, evaluation for therapy-related complications, and detection of symptoms consistent with metastatic disease. As with invasive disease, history and physical examination and routine mammography (if applicable) form the cornerstone of post-treatment surveillance (table 1). Other types of imaging, laboratory tests, and tumor markers should not be routinely obtained. (See "Approach to the patient following treatment for breast cancer".)

APPROACH TO RECURRENT DISEASE

Approximately one-half of all local-regional recurrences are invasive, regardless of treatment approach [5,89,90]. If the recurrence included any invasive disease, it should be treated in a manner appropriate for newly diagnosed invasive breast cancer. (See "Overview of the treatment of newly diagnosed, invasive, non-metastatic breast cancer".)

Locoregional treatment — The treatment for a patient with recurrent DCIS is based upon disease extent, location, and the prior surgical approach (ie, mastectomy versus lumpectomy) (see "Surgery and radiation for locoregional recurrences of breast cancer" and "Systemic therapy for locoregionally recurrent breast cancer"):

- For patients treated with breast-conserving therapy (ie, prior wide local excision plus radiation therapy [RT]), we would perform a mastectomy rather than breast-conserving surgery because these patients are most likely not candidates for further RT. However, in some patients who initially received accelerated partial breast irradiation (PBI), whole-breast irradiation may be feasible, depending on how PBI was previously performed.

- For patients treated with breast-conserving surgery who did not undergo previous RT, options include repeat excision plus RT or mastectomy. A choice between them depends on the extent of disease and patient and provider preferences.

- Although rare, patients who underwent a mastectomy may experience a recurrence in the mastectomy flap. For these patients, we perform wide local excision of the area. These patients should also meet with a radiation oncologist to discuss the role of postexcision RT.

- For patients with an invasive local recurrence after treatment for DCIS, we perform a metastatic work-up. The management of these patients is discussed separately.

Indications for endocrine therapy — Endocrine therapy should be offered as chemoprevention to women with recurrent DCIS who did not previously receive it. (See 'Tamoxifen' above.)

For women who were on tamoxifen and experienced a recurrence of pure DCIS, the benefit of continued tamoxifen following locoregional treatment for recurrent disease is not clear. While some experts prefer to discontinue tamoxifen in these patients, others may prefer to switch to a different endocrine therapy (especially in postmenopausal women) or to continue tamoxifen. In the absence of data to inform a preferred option, the role of endocrine therapy as chemoprevention (for women who experience a recurrence of DCIS while on tamoxifen) should be discussed.

PROGNOSIS

With appropriate treatment, the prognosis for patients with DCIS is excellent. Advancements in screening for DCIS (allowing for early detection, prior to acquisition of high-risk features, and facilitating complete excision), more rigorous and standardized pathologic review and reporting of margins, and adjuvant endocrine therapy have improved outcomes [91].

In an analysis of over 100,000 patients with DCIS enrolled in the Surveillance, Epidemiology, and End Results database, the 20-year breast cancer mortality among women with DCIS was 3.3 percent [3]. The risk of ipsilateral invasive recurrence at 20 years was 5.9 percent, and the risk of contralateral invasive recurrence was 6.2 percent. In this study, predictors of a higher risk of death from breast cancer included young age at diagnosis (before age 35 years, hazard ratio [HR] 2.3, 95% CI 1.6-3.2), high grade (HR 1.88, 95% CI 1.38-2.55), and being from a Black population (HR 2.55, 95% CI 2.17-3.01). Estrogen receptor positivity predicted a lower risk of death (HR 0.53, 95% CI 0.41-0.69).

A separate, prospective, observational study also suggested that risk of recurrence of DCIS decreased with age. Among 2996 patients with DCIS, the HRs for recurrence were as follows, with age <40 years as a reference: for patients age 40 to 49 years, 0.82; 50 to 59 years, 0.46; 60 to 69 years, 0.50; 70 to 79 years, 0.56; and 80 years or greater, 0.21 [92]. This association persisted for cohorts treated either with or without radiation. Ten-year invasive recurrence was 16 percent among those under 40 years versus 6.5 percent for those ≥40 years.

SPECIAL CONSIDERATIONS DURING THE COVID-19 PANDEMIC

The COVID-19 pandemic has increased the complexity of cancer care. Important issues in areas where viral transmission rates are high include balancing the risk from treatment delay versus harm from COVID-19, ways to minimize negative impacts of social distancing during care delivery, and appropriately and fairly allocating limited health care resources. These and other recommendations for cancer care during active phases of the COVID-19 pandemic are discussed separately. (See "COVID-19: Considerations in patients with cancer".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Ductal carcinoma in situ".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Ductal carcinoma in situ (DCIS) (The Basics)")

SUMMARY AND RECOMMENDATIONS

- **Introduction** – Ductal carcinoma in situ (DCIS) of the breast represents a heterogeneous group of neoplastic lesions confined to the breast ducts. The goal of therapy for DCIS is to prevent the development of invasive breast cancer. Therapeutic approaches include surgery, radiation therapy (RT), and adjuvant endocrine therapy. (See 'Introduction' above.)

- **Local treatment**

  - Local therapy for DCIS consists of mastectomy or breast-conserving therapy (BCT). BCT for DCIS includes lumpectomy, generally followed by RT, and results in breast cancer-specific survival rates comparable to mastectomy, although the rate of local recurrence is higher with BCT.

  - Candidates for BCT include patients with DCIS whose disease is localized to an area within one quadrant and can be resected with negative margins in a cosmetically acceptable manner, taking into account the extent of disease relative to the breast size. Re-excision(s), mastectomy, or radiation boost should be performed if close or positive margins are present. (See 'Breast-conserving therapy' above.)

  - For patients who are candidates for BCT, we suggest BCT over mastectomy (**Grade 2B**). We suggest that most women undergoing BCT receive RT in addition to lumpectomy (**Grade 2B**). (See 'Breast-conserving therapy' above.)

    - However, for patients with very small foci of low-grade DCIS, and particularly if it is ER-positive and endocrine therapy will be administered, breast-conserving

surgery only (ie, omission of RT) with widely negative margins (ideally 10 mm) is an option. However, prospective randomized evidence to support the omission of adjuvant radiation is limited, even in selected low-risk cases. (See 'Radiation therapy' above.)

- For most patients with DCIS, we do not perform surgical evaluation of the axilla. However, we pursue sentinel lymph node biopsy in patients who do not meet criteria for BCT and thus require mastectomy. (See 'Indications for SLNB' above.)

- **Systemic treatment**

  - For women with estrogen receptor (ER)-positive DCIS treated with breast-conserving surgery with or without RT, we suggest endocrine therapy rather than observation (**Grade 2B**). For women who opt for treatment, the choice between anastrozole and tamoxifen should be individualized based on the side effect profile of each medication, menopausal status, and the preferences of the patient. (See 'Systemic treatment' above.)

  - In general, for women who undergo unilateral mastectomy for ER-positive DCIS, we suggest endocrine therapy rather than observation (**Grade 2C**). For these patients, the use of endocrine therapy should be considered "chemoprevention" and not treatment to prevent recurrence for this diagnosis. In other words, it would be given with the intent to prevent a new primary contralateral breast cancer. In women having bilateral mastectomies for DCIS, we do not offer chemoprevention, as the risks/adverse events outweigh any potential benefit for risk reduction. (See 'Systemic treatment' above.)

  - We do not routinely utilize tamoxifen as chemoprevention for women with ER-negative DCIS given that the benefit of endocrine therapy does not reduce the risk of recurrence in this population. Some women may opt to take tamoxifen, however, to decrease the risk of developing a new endocrine receptor-positive DCIS or breast cancer. (See 'Tamoxifen' above.)

- **Recurrent disease** – The treatment for a patient diagnosed with a recurrence following original treatment for DCIS is based upon whether the disease is purely in situ or has an invasive component, the disease extent, location, prior surgical approach (ie, mastectomy versus lumpectomy), and whether RT or endocrine therapy was previously administered. (See 'Approach to recurrent disease' above.)

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GRAPHICS

Summary of 2012 ASCO guideline recommendations for surveillance after breast cancer treatment

Mode of surveillance	Recommendation*
Recommended	
History/physical examination	All women should have a careful history and physical examination every three to six months for the first three years after primary therapy, then every 6 to 12 months for the next two years, and then annually. The history and physical examination should be performed by a physician¶ experienced in the surveillance of patients with cancer and in breast examination.
Patient education regarding symptoms of recurrence	Physicians should counsel patients about the symptoms of recurrence including new lumps, bone pain, chest pain, dyspnea, abdominal pain, or persistent headaches. Helpful web sites for patient education include www.cancer.net and www.cancer.org.Δ
Referral for genetic counseling	Women at high risk for familial breast cancer syndromes should be referred for genetic counseling in accordance with clinical guidelines recommended by the US Preventive Services Task Force. Criteria to recommend referral include the following: Ashkenazi Jewish heritage; history of ovarian cancer at any age in the patient or any first- or second-degree relatives; any first-degree relative with a history of breast cancer diagnosed before the age of 50 years; two or more first- or second-degree relatives diagnosed with breast cancer at any age; patient or relative with diagnosis of bilateral breast cancer; and history of breast cancer in a male relative◇.
Breast self-examination	All women should be counseled to perform monthly breast self-examination.
Mammography	Women treated with breast-conserving therapy should have their first posttreatment mammogram no earlier than six months after definitive radiation therapy. Subsequent mammograms should be obtained every 6 to 12 months for surveillance of abnormalities. Mammography should be performed yearly if stability of mammographic findings is achieved after completion of locoregional therapy.
Pelvic examination	Regular gynecologic follow-up is recommended for all women. Patients who receive tamoxifen therapy are at increased risk for developing endometrial cancer and should be advised to report any vaginal bleeding to their physicians. Longer follow-up intervals may be appropriate for women who have had a total hysterectomy and oophorectomy.
Coordination of care	The risk of breast cancer recurrence continues through 15 years after primary treatment and beyond. Continuity of care for patients with breast

	cancer is recommended and should be performed by a physician experienced in the surveillance of patients with cancer and in breast examination, including the examination of irradiated breasts. Follow-up by a PCP seems to lead to the same health outcomes as specialist follow-up with good patient satisfaction. If a patient with early-stage breast cancer (tumor <5 cm and <4 positive nodes) desires follow-up exclusively by a PCP, care may be transferred to the PCP approximately one year after diagnosis. If care is transferred to a PCP, both the PCP and the patient should be informed of the appropriate follow-up and management strategy. Re-referral for further oncology assessment may be considered, as needed, especially for patients who are receiving adjuvant endocrine therapy.
Not recommended	
Routine blood tests	CBC testing is not recommended for routine breast cancer surveillance. Automated chemistry studies are not recommended for routine breast cancer surveillance.
Imaging studies	Chest x-rays are not recommended for routine breast cancer surveillance. Bone scans are not recommended for routine breast cancer surveillance. Ultrasound of the liver is not recommended for routine breast cancer surveillance. CT scanning is not recommended for routine breast cancer surveillance. FDG-PET scanning is not recommended for routine breast cancer surveillance. Breast MRI is not recommended for routine breast cancer surveillance.
Breast cancer tumor marker testing	The use of CA 15-3 or CA 27.29 is not recommended for routine surveillance of patients with breast cancer after primary therapy. CEA testing is not recommended for routine surveillance of patients with breast cancer after primary therapy.

CBC: complete blood count; CEA: carcinoembryonic antigen; FDG-PET: [^{18}F] fluorodeoxyglucose-positron emission tomography; MRI: magnetic resonance imaging; PCP: primary care physician.

* All recommendations remain the same as those published in 2006 *[Khatcheressian JL, Wolff AC, Smith TJ, et al. American Society of Clinical Oncology 2006 update of the breast cancer follow-up and management guidelines in the adjuvant setting. J Clin Oncol 2006; 24:5091]*. The Panel concluded that there was no new evidence that warranted changing any of the recommendations. The 2006 guideline provides a detailed discussion and rationale for the recommendations.

¶ Although the evidence is lacking, it seems likely that history as well as physical and breast exams may also be conducted by experienced non-physician providers (eg, nurse practitioners, physician assistants) under the supervision of an experienced physician.

Δ UpToDate also offers free patient information content: www.uptodate.com/patients.

◇ Expert consensus-based recommendations are available with criteria specific to patients with cancer (eg, from the National Comprehensive Cancer Network [www.nccn.org]). These recommendations include similar criteria as those from the US Preventive Services Task Force as

well as other criteria such as diagnosis of triple negative breast cancer, or a combination of breast cancer and other specific cancers.

Khatcheressian JL, Hurley P, Bantug E, et al. Breast Cancer Follow-Up and Management After Primary Treatment: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 2013; 31:961. Reprinted with permission.

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Contributor Disclosures

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