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Controversies in the Treatment of DCIS

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Abstract

Ductal carcinoma in situ (DCIS) accounts for 20% of all newly diagnosed breast cancers. Mastectomy was once the gold standard for the treatment of DCIS; however, breast-conserving surgery (BCS) has been adopted as the treatment of choice for patients with small, screen-detected lesions. Both adjuvant radiation and hormonal therapy following BCS have been demonstrated in randomized trials to reduce the risk of invasive recurrence, but neither affects survival. With the variety of surgical and adjuvant treatment options available, there has been great interest in tailoring the treatment to the individual, with the goal of optimizing the balance of risks and benefits according to the values and priorities of the woman herself. Prospective studies of women with "low-risk" DCIS have successfully identified women at lower than average risk, but have not achieved the goal of identifying a subset of women with DCIS at minimal risk of recurrence after surgical excision alone.

Keywords

ductal carcinoma in situ; surgery; radiation; endocrine therapy; local recurrence; margin width; risk estimation

INTRODUCTION

Prior to the routine use of screening mammography, ductal carcinoma in situ (DCIS) comprised only 1–2% of all breast cancers (1). With the widespread adoption of screening mammography, the incidence of DCIS has dramatically increased over the past 3 decades, now accounting for 20% of all newly diagnosed breast cancers (2). Approximately 61,000 new cases of DCIS are expected to be diagnosed in the United States in 2016 (2).

Four prospective randomized trials of adjuvant radiation (RT) after breast-conserving surgery (BCS) for DCIS, begun between 1985 and 1990, demonstrated that women treated with BCS alone had a substantial risk of local recurrence, ranging from 26% to 36% at 13–

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20 years of follow-up (3–6). These trials, along with National Surgical Adjuvant Breast and Bowel Project (NSABP) B-24, a randomized trial of tamoxifen use for women with DCIS treated with BCS and RT, established that RT and endocrine therapy following BCS decreased the rate of local recurrence by approximately 50% and 30%, respectively (3–7).

Beginning in the late 1990s, 3 additional prospective studies examined outcomes following BCS in selected women with low-risk DCIS. Wong et al reported 10-year local recurrence rates after BCS alone of 15.6% (8). In the Eastern Cooperative Oncology Group-American College of Radiology Imaging Network (ECOG-ACRIN) E5194 study, Solin et al found a 10-year local recurrence rate of 12.5%, with tamoxifen given to 30% of the women (9). McCormick et al recently reported 7-year local recurrence rates of 6.7%, with 62% taking tamoxifen (10).

The mortality from DCIS is low. A recent retrospective examination of women with DCIS treated with mastectomy or BCS, with or without radiation, in the Surveillance, Epidemiology, and End Results (SEER) 18 registries research database found a 3% breast cancer mortality rate at 20 years of follow-up (11). In the 4 mature randomized trials, breast cancer mortality was approximately 2–5% at about 15 years of follow-up (3–6). Because survival after surgical treatment is excellent and neither RT nor tamoxifen therapy improves survival (3–7), there are concerns about the appropriate use of RT and endocrine therapies, each of which has potential morbidities. Therefore, significant controversy exists regarding the appropriate balance between risks and benefits of various treatments for DCIS.

POTENTIAL FOR PROGRESSION TO INVASIVE CARCINOMA

DCIS is defined as a malignant proliferation of ductal epithelial cells that are confined to the milk duct. The structural boundary that distinguishes in situ from invasive breast cancer is the basement membrane (12). The coexistence of DCIS and invasive carcinoma within one lesion suggests that DCIS acts as a precursor lesion to invasive carcinoma. Furthermore, among patients treated with BCS who experience a local recurrence, half of those recurrences are invasive (7), with similarities in morphology and immunohistochemical and genetic profiles between the invasive and in situ cancers (13, 14).

Autopsy Studies

Several autopsy studies have reported that the prevalence of DCIS exceeds that seen in the general population, suggesting that a substantial disease “reservoir” of DCIS exists that may not become clinically significant (15). A review of 7 autopsy series of women not known to have breast cancer by Welch et al reported a median prevalence (number of women diagnosed with DCIS/number of women examined) of DCIS of 8.9% (range 0–14.7%) (15). The wide variability in DCIS detection among autopsy studies may be attributed to difference in tissue sampling, with studies examining anywhere from 9 to 275 slides per breast (15); the highest prevalence occurred in studies which examined more slides per breast. The findings of DCIS at autopsy suggest that there is a significant reservoir of undiagnosed DCIS that does not become clinically apparent before death. However, this is not surprising given the known long clinical course of breast cancer in general and DCIS in particular; recurrence of DCIS after excision continues even after 15 years of follow-up (3–

6). Such autopsy studies provide little insight into the natural history of DCIS that is clinically diagnosed in a woman with a substantial life expectancy; only longitudinal studies evaluating rates of subsequent development of invasive carcinoma can shed light on the clinical importance of DCIS.

Outcomes for Women with DCIS after Surgical Biopsy Alone

The only available evidence regarding the natural history of DCIS comes from published reports of benign excisional biopsy specimens that were re-reviewed decades later and found to contain DCIS. Rosen et al reviewed histologic sections from over 10,000 benign surgical excisional biopsies performed at Memorial Sloan Kettering Cancer Center from 1940 to 1950 and identified 30 cases with microscopic findings of untreated low-grade DCIS. At an average follow-up of 18 years for the 15 patients in whom follow-up was available, 8 (53%) had developed invasive carcinoma in the same breast as the initial DCIS lesion, at an average interval of 9.7 years after the surgical biopsy (16, 17).

A similar study by Page et al (18), updated by Sanders et al (19), reported 31-year follow-up of 28 women with small, low-grade, non-comedo DCIS diagnosed on re-review many years after undergoing a benign surgical biopsy. Eleven (39%) women developed invasive breast cancer in the same quadrant as their original low-grade DCIS.

A nested case-control study of 1877 breast biopsy specimens from the Nurse's Health Study identified 13 cases of DCIS that were originally diagnosed as benign, of which 2 of 4 with low-grade, 2 of 6 with intermediate-grade, and 2 of 3 with high-grade DCIS developed ipsilateral invasive cancer a mean of 9 (range 4–18) years after the initial "benign" biopsy (20). In all, 6 (46%) developed ipsilateral invasive breast cancer and 4 (31%) developed ipsilateral DCIS subsequent to the initial "benign" biopsy. The odds ratio (OR) for the development of invasive breast cancer in women with a missed diagnosis of DCIS in the breast biopsy compared to those with benign disease was 13.5 (95% confidence interval [CI] 3.7–49.7) (20).

These studies demonstrate that the risk of progression to invasive carcinoma in patients with unrecognized DCIS that underwent "benign" surgical excisional biopsy is substantial (39%–53%). Further, these rates may be an underestimate of the risk of progression given that the undiagnosed DCIS may have been completely excised in at least some cases. Furthermore, the presence of low-grade histology in these patients was not predictive of a benign clinical course. Taken together, these data support the hypothesis that DCIS is a precursor lesion.

Progression to Invasive Carcinoma after Standard Treatment in Prospective Studies

Evidence for progression of DCIS to invasive carcinoma also comes from prospective studies evaluating the incidence and type of in-breast tumor recurrence (IBTR) after BCS. In all randomized studies of adjuvant therapies, at all reported time points, approximately half of all ipsilateral recurrences were invasive at the time of diagnosis (3–7, 10). If it is assumed that recurrences are due to undetected and unresected DCIS that remains in the breast after both surgical excision and adjuvant therapies, then this suggests that at least half of DCIS has the potential to progress to invasive carcinoma.

In addition, if DCIS were simply a marker of increased risk, the expected incidence of invasive cancer should be similar in the ipsilateral and contralateral breast. However, in the meta-analysis of the mature randomized trials of RT after BCS, ipsilateral invasive recurrence occurred in 204 of 1851 (11%) ipsilateral breasts allocated to BCS alone as compared to only 56 (3%) contralateral breasts (7).

Finally, if DCIS were a high-risk lesion, then margins of resection would be unimportant at the time of lumpectomy and would not affect local control. However, the meta-analysis of the randomized trials demonstrated that in patients treated with lumpectomy alone, the 10-year risk of an IBTR was markedly higher in patients with positive vs. negative margins (43.8% vs. 26.0%); this was also true in patients receiving RT with a 10-year IBTR rate of 24.2% vs. 12.0% in patients with positive vs. negative margins (7).

STANDARD TREATMENT OPTIONS FOR DCIS

Several standard treatment options exist for DCIS, including mastectomy, BCS alone, BCS with RT, BCS with endocrine therapy, and BCS with both RT and endocrine therapy. Although survival is excellent with each treatment option, the rates of local recurrence vary widely between the different treatments (7, 11, 21).

Mastectomy

Before the 1990s, mastectomy was considered the gold standard for the treatment of DCIS. Following mastectomy, the theoretical risk of local recurrence of a purely in situ lesion should be essentially zero. However, a low rate of local recurrence has been documented, with a study level meta-analysis of 8 retrospective studies demonstrating an adjusted 10-year local recurrence rate of 2.6% (95% CI 0.8–4.5%) (21). As a pre-invasive lesion, mastectomy may be overtreatment for many women with small, localized DCIS. Women considering mastectomy should be counseled regarding the increased surgical complication rate associated with mastectomy compared to BCS (22) and the possible impact on body image and sexual functioning post-surgery (23).

Breast-Conserving Surgery

After randomized trials proved that BCS was equivalent to mastectomy in women with invasive cancer (24–29), BCS became an acceptable treatment option for early-stage disease. Although there were no randomized prospective trials comparing recurrence and overall survival between mastectomy and BCS in DCIS, in the late 1980s clinicians extrapolated from the findings for invasive cancer and began adopting BCS for DCIS. A non-randomized retrospective study by Silverstein et al compared 227 patients with DCIS treated with mastectomy or BCS (with or without RT); despite an imbalance between the groups (with patients with larger tumors receiving mastectomy), the 7-year disease-free survival (DFS) was 98% for mastectomy and 84% for BCS, with no difference in overall survival (OS) (30).

Adjuvant Radiation

From 1985 to 1990, 4 prospective randomized trials comparing adjuvant RT to no RT following BCS for DCIS were initiated to determine the most appropriate treatment for

women with small localized DCIS (3–6) (Table 1). The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) performed an individual patient-level meta-analysis of the 4 randomized trials which included 3729 women. The addition of RT after local surgical excision reduced the recurrence risk by about 50%, corresponding to an absolute 10-year reduction in risk of any ipsilateral breast recurrence of 15.2% (28.1% [no RT] vs. 12.9% [RT], $p < 0.00001$) (7). In all patient subsets, including those with small, low-grade tumors and negative margins, RT reduced the risk of an ipsilateral breast event by approximately half. In addition, the risk of invasive recurrence was approximately halved with RT, with Wapnir et al reporting a 15-year incidence of invasive IBTR of 19.4% [no RT] vs. 8.9% [RT] (5).

The use of RT did not, however, improve breast cancer mortality (3.7% [no RT] vs. 4.1% [RT], p = NS) or all-cause mortality (8.2% [no RT] vs. 8.4% [RT], p = NS) (7). RT is not without risk and can be associated with increased rates of rare malignancies and cardiovascular disease (31, 32). With no documented improvement in survival with the use of RT in DCIS patients, these potential side effects should be weighed against the reduction in local recurrence when making treatment recommendations for patients with DCIS.

Adjuvant Endocrine Therapy

The addition of tamoxifen following local excision of DCIS (with or without RT) has also been shown to decrease the risk of local recurrence in 2 randomized trials. The NSABP B-24 trial randomized 1804 women with DCIS treated with BCS and RT to tamoxifen vs. placebo for 5 years. Unlike NSABP B-17, where all patients had tumor-free margins, approximately 25% of patients had involved or uncertain margins in B-24. The 15-year cumulative incidence of IBTR was reduced from 18.3% to 16.0% with the addition of tamoxifen, with a reduction in invasive IBTR from 10% to 8.5%. Interestingly, the addition of tamoxifen seemed to largely offset the effect of a positive margin, with no significant difference in invasive (p = 0.4) or DCIS (p = 0.31) IBTR between tamoxifen-treated patients with involved vs. tumor-free margins (5).

The UK, Australia, and New Zealand (UK/ANZ) DCIS trial was a 2×2 factorial randomized trial of both RT and tamoxifen, with women offered a choice of participating in either or both randomizations. 1576 women entered the tamoxifen randomization, of whom 1053 did not receive RT and 523 did receive RT. Tamoxifen reduced the incidence of all new breast events (hazard ratio [HR] 0.71, 95% CI 0.58–0.88; p = 0.002), with significant reductions in ipsilateral DCIS recurrence (HR 0.70, 95% CI 0.51–0.86; p = 0.03) and any contralateral breast cancer event (HR 0.44, 95% CI 0.25–0.77; p = 0.005). When stratified by receipt of RT, the ipsilateral benefit of tamoxifen was limited to those not receiving RT (HR for ipsilateral breast events 0.77, 95% CI 0.59–0.98; p = 0.04) and was not significant in those receiving RT (HR for ipsilateral breast events 0.93, 95% CI 0.5–1.75; p = 0.8). Tamoxifen had no effect on ipsilateral invasive disease overall (HR 0.95, 0.66–1.38; p = 0.8), or after stratification by use of RT (3).

The overall reduction in risk of all breast events (ipsilateral and contralateral) due to tamoxifen was similar in the 2 trials: 29% in the UK/ANZ trial (3) and 27% in NSABP B-24 (5). However, in B-24, all women received radiation and there was a 32% relative reduction

in ipsilateral invasive recurrence (p = 0.025) (5). In contrast, the UK/ANZ trial found no significant decrease in ipsilateral invasive recurrence (HR 0.95; p = 0.79), and the observed reduction in all ipsilateral breast events was limited to those not receiving RT (3).

Patients were enrolled in NSABP B-24 and the UK/ANZ trial without knowledge of hormone receptor status. Allred et al subsequently tested a subset of 732 cases (41%) from B-24 for estrogen receptors. They found that the benefit of tamoxifen was limited to the estrogen receptor positive group, and in this subset tamoxifen was associated with a 42% reduction in any breast event (p = 0.0015), a 47% reduction in any invasive breast cancer (p = 0.005), and a 32% reduction in any ipsilateral breast cancer (p = 0.07) (33).

Neither B-24 nor UK/ANZ showed an improvement in survival with the use of adjuvant tamoxifen. Wapnir et al reported similar 15-year breast cancer death rates with placebo (2.7%) and tamoxifen (2.3%) (5). The UK/ANZ trial also reported low breast cancer death rates of 2% (no adjuvant treatment), 3% (tamoxifen), 1% (radiation), and 2% (radiation and tamoxifen) and noted that “deaths from breast cancer seemed to be slightly higher in the tamoxifen group, but this difference was not significant” (3).

The recently published NSABP B-35 and International Breast Cancer Intervention Studies (IBIS)-II trials compared anastrozole to tamoxifen in postmenopausal women with hormone receptor positive DCIS treated with local excision (34, 35). Both were randomized double-blind studies; radiotherapy was administered to all 3104 women in B-35, and to 71% of the 2980 women in IBIS-II. In B-35, the 10-year breast cancer event rate was 6.9% among those randomized to anastrozole vs. 10.9% in the tamoxifen group, corresponding to a hazard ratio of 0.73 (p = 0.02) with anastrozole. In IBIS-II, at a median follow-up of 7.2 years, the incidence of any breast cancer event was low in both groups (5%), and anastrozole was demonstrated to be non-inferior (34). In both NSABP B-35 and IBIS-II, the overall proportion of patients with adverse events was similar between anastrozole and tamoxifen, but the type of side effects varied by treatment (Table 2) (34, 35). The high frequency of patient-reported adverse events can reduce patient compliance with endocrine treatment.

Although the addition of endocrine therapy does reduce the incidence of recurrence after excision for DCIS, many patients experience an adverse event; without a survival benefit, the threshold to discontinue endocrine therapy should be low, especially in the setting of significant side effects.

RISK FACTORS FOR LOCAL RECURRENCE

As shown in the randomized trials discussed above, local recurrence after local excision for DCIS can be reduced by at least half with the addition of adjuvant therapies. But not all patients with DCIS have a similar risk of local recurrence, and therefore they do not garner the same absolute benefit with adjuvant therapy. Although the randomized trials failed to identify a subset of “low-risk” patients who did not benefit from adjuvant RT, there has been ongoing interest in finding low-risk subsets of DCIS in whom the absolute benefit of RT or other adjuvant therapy is small. Conversely, there is a need to identify those at high risk of invasive recurrence so that their risk can be minimized by appropriate treatment.

Treatment Period

The first 4 randomized DCIS trials evaluating RT were begun in the late 1980s and found that at 13–20 years of follow-up, women treated with BCS alone had a risk of local recurrence ranging from 26%–36% compared to 9%–23% after BCS with adjuvant RT (3–6). Two prospective single-arm studies of BCS alone that began in the late 1990s selected women with low-risk DCIS and reported lower 10-year recurrence rates, ranging from 12.5%–15.6% (8, 9). Most recently, McCormick et al recently reported 7-year local recurrence rates of 6.7% among women with low-risk DCIS treated with BCS, of whom 62% took tamoxifen (10).

Thus it appears that the incidence of local recurrence following excision for DCIS has declined over time. In a recent retrospective analysis of 2996 DCIS patients undergoing BCS at Memorial Sloan Kettering Cancer Center from 1978–2010, a significant decrease in recurrence rates over time was observed ($p = 0.001$). Five- and 10-year recurrence rates significantly decreased, from 13.6% (5-year) and 20% (10-year) in women treated from 1978–1998, to 6.6% and 14%, respectively, in women treated from 1999–2010 ($p < 0.0001$). Even after controlling for multiple other factors associated with recurrence, treatment period was significantly associated with recurrence, with a lower risk of recurrence in the later time period (HR 0.74; $p = 0.02$) compared with the earlier time period. After stratifying by use of RT, treatment period remained associated with recurrence in those not receiving RT, suggesting that advances in radiation technique could not explain the decline (36). It is likely that factors such as improvements in radiologic detection and pathologic assessment have contributed to the observed decrease in recurrence rates (7, 36).

Age

Younger age has also been demonstrated to be associated with a higher risk of local recurrence for DCIS treated with BCS in both retrospective studies (37, 38) and in the randomized studies of RT (3–7). Recently, Cronin et al evaluated the relationship between age and recurrence across the full spectrum of age in a large cohort of almost 3000 patients with DCIS treated with BCS. The absolute rates of local recurrence fell with older age ($p < 0.0001$), with 10-year rates of 27.3% in women < 40 years of age as compared to 7.5% in women ≥ 80 years of age. On multivariable analysis, after adjusting for 8 clinicopathologic and treatment variables, risk of recurrence decreased with increasing age (HRs with < 40 years of age as reference: 40–49 years of age [0.82, $p = 0.36$], 50–59 years of age [0.46, $p = 0.0005$], 60–69 years of age [0.50, $p = 0.003$], 70–79 years of age [0.56, $p = 0.02$], ≥ 80 years of age [0.21, $p = 0.0015$]). In addition, women < 40 years of age were at particularly higher risk for invasive recurrence; 10-year rates of invasive recurrence were 15.8% vs. 6.5% for those < 40 years of age vs. ≥ 40 years of age (39). The effect of a woman's age on her recurrence risk should be included in the discussion of the risks and benefits of the various options for treatment. There is no evidence of any survival difference with any appropriately selected treatment option, and the impact on quality of life with the various options will vary in different women.

Margin Width

Of all the various risk factors for recurrence of DCIS, margin width is the only potentially modifiable factor. The randomized prospective trials of RT have shown that positive margins are associated with a higher risk of recurrence after BCS (4–7). Specifically, among patients enrolled in NSABP B-24 (lumpectomy and RT +/− tamoxifen), a study where 25% of patients had involved or unknown margins, the HR for invasive recurrence in BCS patients treated with RT with positive vs. negative margins was 2.61 (95% CI 1.68–4.05, $p < 0.001$) (5). However, because margin status was dichotomized as positive or negative in the randomized trials, these studies cannot be used to determine the optimal negative margin width.

Van Zee et al recently evaluated the association between margin width and local recurrence in a large population of DCIS patients treated with BCS over a 30-year period. Overall, among nearly 3000 DCIS patients, a trend toward lower risk of recurrence was associated with wider margins ($p = 0.087$). The 10-year rate of recurrence was 31% for women with positive margins (most had only focally positive margins) compared to 13% for women with margins > 10 mm. On multivariable analysis, after controlling for clinicopathologic and treatment factors associated with recurrence, wider margins were associated with a lower risk of recurrence for the entire population (HR 0.44 for > 10 mm margins as compared to positive margins; $p = 0.0003$). In those not receiving RT, the association between margin width and recurrence was strong ($p < 0.0001$), whereas for those receiving RT, there was no clear relationship ($p = 0.95$) (40).

As a result of the lack of consensus regarding optimal margin width for DCIS, a consensus conference was recently convened and a study level meta-analysis of the literature regarding margin width for DCIS was completed. The results of this work should help inform clinicians as to the negative margin width that optimizes outcomes for DCIS.

STUDIES OF BREAST-CONSERVING SURGERY FOR LOW-RISK SUBSETS OF DCIS

The randomized prospective trials of DCIS have demonstrated that RT reduces the risk of developing a local recurrence and invasive local recurrence following BCS by approximately 50% in all identified subgroups (7), but most patients treated with local excision alone will never develop a local recurrence. Recurrence rates for those treated without RT in the early randomized trials were high, approximately 30% at 10 years (7). However, recurrence rates following BCS for DCIS have steadily declined since the initiation of the 4 randomized RT trials (36), and identification of a subset of DCIS patients with a low absolute risk of local recurrence in whom RT may be omitted has been an area of great interest.

Wong et al prospectively accrued 143 patients between 1995 to 2002 with predominantly low- to intermediate-grade DCIS ≤ 2.5 cm undergoing BCS without RT and with margins ≥ 1 cm. They reported a 10-year local recurrence of 15.6%. None used tamoxifen. Although the authors concluded that the risk of local recurrence was “substantial and ongoing” over

time, the 10-year risk was still substantially lower than the 28.1% 10-year risk reported from the earlier randomized trials (7, 8).

The prospective ECOG-ACRIN E5194 single-arm study of BCS without RT enrolled patients between 1997 and 2002. Tamoxifen was given to 30% of patients. Patients with low/intermediate grade DCIS measuring ≤ 2.5 cm and with ≥ 3 mm margins, had a 12-year local recurrence rate of 14.4% (95% CI 11.2%–17.6%), while patients with high-grade DCIS measuring ≤ 1 cm with ≥ 3 mm margins had a 12-year local recurrence rate of 24.6% (95% CI 15.7%–33.4%) (9). The 12-year invasive local recurrence rates were 7.5% (low/intermediate grade cohort) and 13.4% (high-grade cohort). The authors concluded that "individual patients and their physicians will need to decide if these 12-year risks are acceptable, and to judge whether or not to add adjuvant treatment after surgical excision" (9).

Between 1998 and 2006, McCormick et al randomized 636 patients to RT or not. The eligibility criteria were the same as the low/intermediate grade cohort from the ECOG E5194 study, but 62% of the women took tamoxifen. At 7 years, the local recurrence rate was 0.9% (95% CI 0.0%–2.2%) in the RT arm vs. 6.7% (95% CI 3.2%–9.6%) in the observation arm (10). The absolute low risk of local recurrence following local excision in carefully selected patients with "low-risk" DCIS suggests that RT for all patients with DCIS should not be mandatory; estimation of local recurrence risk is paramount in making appropriate decisions regarding adjuvant RT.

PREDICTING RISK OF LOCAL RECURRENCE

Estimation of risk of recurrence after treatment for DCIS can assist a woman in the decision-making process regarding the multitude of options available to her. Knowing that there are several clinicopathologic factors associated with risk of recurrence, Rudloff et al developed a nomogram that incorporates 10 different factors to better estimate risk of recurrence for DCIS treated with BCS (41). From 1991 to 2006, 1681 consecutive patients with DCIS treated with BCS were utilized to construct a nomogram that integrates 10 clinical, pathologic, and treatment variables to estimate the risk of local recurrence at 5 and 10 years after BCS. The model was internally validated using bootstrapping and showed good discrimination (C-index, 0.704; bootstrap corrected 0.688) (41). The DCIS nomogram has subsequently been applied to several external independent populations and shown to have good discrimination (C-index, 0.63–0.69) (42–45). Further, and perhaps more importantly, the calibration of the nomogram has been shown to be excellent. For example, Collins et al found the overall correlation between the 5- and 10-year nomogram-predicted and observed recurrences was 98% and 95%, respectively (42). For the lowest nomogram-predicted quartile of patients, the 5-year risk was 4.8% (95% CI 3.1–6.4%), as compared to the highest quartile, which was 33.1% (95% CI 24.2–40.9%, $p < 0.0001$) (42).

The Oncotype DX (Genomic Health, Redwood City, CA) DCIS score is a 12-gene assay developed to quantify local recurrence risk and invasive local recurrence risk in patients treated with BCS. The DCIS score was validated using the ECOG E5194 study; 327 patients had sufficient tissue for analysis. The DCIS score was statistically associated with the risk of

developing a local recurrence (HR 2.31, p = 0.02) and an invasive local recurrence (HR 3.68, p = 0.01). The 10-year risk of local recurrence for low-, intermediate-, and high-risk groups was 10.6%, 26.7%, and 25.9%, respectively ($p \leq 0.006$). On multivariable analysis, tumor size and menopausal status remained statistically significantly associated (p = 0.01 tumor size, p = 0.02 menopausal status) with local recurrence even when the DCIS score (p = 0.02) was included, demonstrating that other clinical factors remain as important as the score in estimating risk of recurrence (46). The DCIS score was also applied to a population-based cohort of 718 patients with DCIS treated with BCS with tumor-free margins from 1994 to 2003 and was found to be significantly associated with local recurrence (p = 0.02) (47). However, the magnitude of the effect (i.e., hazard ratio) of age, multifocality, tumor size, and DCIS architecture were all greater than that of the DCIS score. For example, for women < 50 years of age with multifocal DCIS, a “low” score was associated with at 30% 10-year recurrence risk, and for women ≥ 50 years of age, with DCIS ≤ 1.5 cm, a “high” score was associated with a 10% 10-year recurrence risk (48). Notably, for either overall or invasive recurrence risk, an “intermediate” score was associated with an empirically higher rate of recurrence than a “high” score: 10-year rates of any local recurrence in the low-, intermediate-, and high-risk groups were 13%, 33%, and 28%, respectively, and for invasive local recurrence, 8, 21%, and 15.5%, respectively (47).

PROSPECTIVE STUDIES OF OBSERVATION IN LOW-RISK DCIS

Currently, there are 2 ongoing studies evaluating surgery vs. observation in women with low-risk DCIS. The Surgery versus Active Monitoring for Low-Risk DCIS (LORIS) trial is studying the safety of observation alone for a select cohort of patients with non-high–grade DCIS diagnosed by core needle biopsy. LORIS eligibility criteria include women age ≥ 46 years with screen-detected calcifications and non-high–grade DCIS diagnosed by vacuum assisted core needle biopsy. The primary outcome of the study is invasive breast-cancer–free survival at 5 years among women randomized to observation alone or to standard surgical and adjuvant treatment (49). The Low Risk DCIS (LORD) trial is a randomized, international, multicenter, phase III non-inferiority trial comparing active surveillance versus standard surgical therapy for screen-detected, low-grade DCIS. Eligibility criteria are similar to the LORIS trial and include women ≥ 45 years of age with screen-detected calcifications and low-grade DCIS diagnosed by vacuum-assisted core needle biopsy. The primary endpoint is ipsilateral invasive breast cancer-free survival at 10 years (50).

When assessing the safety of observation for patients with low-risk DCIS, it is essential that the patient have a low risk of harboring occult invasive disease. A recent study by Pilewskie et al evaluated 296 LORIS-eligible patients diagnosed with DCIS by core needle biopsy between 2009 and 2012; of these, 20% had invasive carcinoma at surgical excision that was heterogeneous in grade, size, and receptor status (51). Therefore, until further risk stratification can identify patients who may be at low risk for upgrade to invasive carcinoma, patients with core biopsy-proven DCIS should not be considered for observation outside of a clinical trial.

In an attempt to estimate the minimum rate of local recurrence among women in the LORIS trial, Pilewskie et al also assessed 10-year recurrence rates in women with DCIS that

fulfilled all eligibility requirements for LORIS, but also had complete surgical excision (52). Among the women who did not receive RT, and whose lesions were completely excised and were proven to not contain any invasion or foci of high-grade DCIS upon complete examination of the surgical excision specimen, the 10-year rate of any IBTR was 12.1% and invasive IBTR was 6% (52).

TO TREAT OR NOT TO TREAT

A recent retrospective study by Narod et al evaluated 10- and 20-year breast cancer-specific mortality among 108,196 women with DCIS identified from the SEER database. The 20-year breast cancer mortality was 3.3%, with no significant difference in mortality based on treatment received (11). Of note, all women underwent treatment appropriate for their clinical situation, according to clinical judgment and patient preference; treatment was not assigned in a randomized fashion. Furthermore, all patients received treatment, and it is likely that women with higher-risk disease generally received more aggressive treatment. Nevertheless, this retrospective, non-randomized study has been misinterpreted by some as evidence that DCIS is an entity that does not require treatment, and that all treatments result in similar outcomes. While it is true that DCIS is a heterogeneous disease with a poorly understood natural history, the evidence supporting DCIS as a precursor to invasive carcinoma is strong and supported by prospective studies, and proof of safety of observation without surgical excision is lacking. In fact, although combining clinical factors does allow identification of a group of women with DCIS that is at a relatively low risk of recurrence after complete surgical excision (8–10), the ability to safely predict that a particular DCIS lesion will not invade when left in situ remains an unreached goal.

The treatment for DCIS is no longer a “one-size-fits-all” approach. In judging the “best” treatment option for an individual, an individual’s priorities are paramount in choosing the most appropriate treatment plan. The goal of the physician is to inform the discussion and decision making by presenting historic and modern data, so that a truly informed decision can be made regarding the various options. Because RT has been shown to reduce the risk of local recurrence by half following BCS, but has no impact on breast cancer mortality, it is difficult to make a recommendation that all women with DCIS should get RT, particularly since RT also carries rare but potentially serious risks. Similarly, although endocrine therapy reduces ipsilateral and contralateral events, there is no evidence of a survival advantage and there are risks associated with both tamoxifen and aromatase inhibitors. Further, although there is a clearly lower rate of recurrence with mastectomy as compared to BCS, any theoretical survival benefit would be very small, and mastectomy can have a negative impact on quality of life.

We believe that the optimal approach to counseling patients with DCIS is to have a thorough discussion of the options, including the relative importance to that individual woman of the various risks and benefits associated with each treatment. An estimate of risk can assist her in weighing the pros and cons according to her own values, so that she can choose the treatment that is best for her.

Acronyms and Definitions

DCIS	ductal carcinoma in situ
BCS	breast-conserving surgery
IBTR	in-breast tumor recurrence
RT	radiation

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Summary of Points

1. Half of ductal carcinoma in situ (DCIS) recurrences are invasive, with similarities in morphology and genetic profiles between invasive and in situ cancers, providing support that DCIS is a precursor to invasive carcinoma.
2. Radiation therapy reduces the risk of local recurrence after breast-conserving surgery for DCIS by half, but can be associated with rare but serious side effects.
3. Endocrine therapy reduces the risk of local recurrence after breast-conserving surgery and RT by about 30%; however, many patients experience side effects with therapy, which reduces compliance.
4. Mortality from DCIS is low (approximately 2–5%) following appropriate surgical treatment with mastectomy or breast-conserving surgery (with or without radiation).
5. Local recurrence rates following breast-conserving surgery have declined over time, likely due to improvements in radiologic detection and pathologic assessment.
6. Young age (< 40 years) is associated with a higher risk recurrence, and especially invasive recurrence, following breast-conserving surgery, whilst older age (> 80 years) is associated with a lower risk of any recurrence.
7. Individualized risk prediction tools can assist in estimating risk of recurrence for a woman undergoing breast-conserving surgery for DCIS.
8. The optimal approach to counseling patients with DCIS includes weighing the risks and benefits of the various treatment options, so that the best treatment option for the individual is chosen.

Table 1

Review of randomized trials comparing breast-conserving surgery (BCS) with or without adjuvant radiation (RT)

					Local recurrence	
Study name	**Study dates**	**N**	**Median F/U[a] (years)**	**% positive/unknown margins**	**No RT**	**RT**
NSABP[b] B-17 (5)†	1985–1990	818	17.25	0%	35.1%	17.7%
EORTC[c] 10853 (4)†	1986–1996	1010	15.8	16%	31.0%	18.0%
SweDCIS[d] (6)‡	1987–1999	1067	17.5	20%	32.0%	20.0%
UK/ANZ DCIS[e] (3)§	1990–1998	1030	12.7	0%	19.4%	7.1%

† 15-year local recurrence rates

‡ 20-year local recurrence rates

§ 10-year local recurrence rates

[a] Abbreviation: F/U, follow-up

[b] Abbreviation: NSABP, National Surgical Adjuvant Breast and Bowel Project

[c] Abbreviation: EORTC, European Organisation for Research and Treatment of Cancer

[d] Abbreviation: SweDCIS, Swedish Ductal Carcinoma in Situ

[e] Abbreviation: UK/ANZ DCIS, UK, Australia, and New Zealand Ductal Carcinoma In Situ

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Table 2

Adverse events associated with endocrine therapy in the NSABP[a] B-35 and IBIS[b]-II trials

NSABP B-35[†]				
	Anastrozole	**Tamoxifen**	**OR[c] (95%CI[d])**	**P value**
	N=1539	N=1538		
Endometrial cancer	8 (0.5%)	17 (1.1%)	0.47 (0.18–1.15)	NS[e]
Osteoporotic fractures	69 (4.4%)	50 (3.3%)	1.38 (0.95–2.03)	NS
Arthralgia[≠]	504 (33%)	358 (23%)	–	–
Thromboembolic events[≠]	12 (0.8%)	41 (2.7%)	–	–
IBIS-II				
	Anastrozole	Tamoxifen	OR (95% CI)	P value
	N=1449	N=1489		
Endometrial cancer	1 (0.06%)	11 (0.7%)	0.09 (0.002–0.64)	0.0044
Osteoporotic fractures	129 (9%)	100 (7%)	1.36 (1.03–1.80)	0.027
Arthralgia	832 (57%)	729 (49%)	1.41 (1.21–1.63)	< 0.0001
Hot flashes	818 (56%)	899 (60%)	0.85 (0.73–0.99)	0.031
Vaginal dryness	189 (13%)	159 (11%)	1.25 (1.00–1.58)	0.047
Vaginal discharge	30 (2%)	136 (9%)	0.21 (0.14–0.32)	< 0.0001
Thromboembolic events	7 (< 1%)	24 (2%)	0.30 (0.11–0.71)	0.0028
Cardiovascular events	93 (6%)	84 (6%)	1.15 (0.84–1.57)	0.38
Cataracts	72 (5%)	61 (4%)	1.22 (0.85–1.77)	0.26

[†] p values were not included for NSABP B-35

[≠] information about adverse events available for 3070 patients (1535 in each treatment arm)

[a] Abbreviation: NSABP, National Surgical Adjuvant Breast and Bowel Project

[b] Abbreviation: IBIS, International Breast Cancer Intervention Studies

[c] Abbreviation: OR, odds ratio for women in the anastrozole group compared with those in the tamoxifen group

[d] Abbreviation: CI, confidence interval

[e] Abbreviation: NS, non-significant

Adapted with data from Margolese et al and Forbes et al (34, 35).

Note to Editor: This table was created by the authors using data from these 2 cited references. If permission to do so is required beyond this credit line, please notify the authors.