Are There Alternative Strategies for the Local Management of Ductal Carcinoma in Situ?

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KEYWORDS

• Ductal carcinoma in situ (DCIS) • Active surveillance • Endocrine therapy

KEY POINTS

- Ductal carcinoma in situ (DCIS) is currently treated in similar ways to invasive breast cancer.
- Given the excellent breast cancer–specific survival for women with a diagnosis of DCIS, less invasive strategies than current therapy merit evaluation.
- Active surveillance of appropriately selected women with low-risk DCIS is the subject of several randomized clinical trials.
- Outcomes of invasive breast cancer and patient-reported outcome measures may change the way women with low-risk DCIS are managed in future.

INTRODUCTION

The management of ductal carcinoma in situ (DCIS) has largely shadowed the treatment of invasive breast cancer: surgical excision with adjuvant radiation and endocrine therapy for the prevention of further in situ or invasive events. As for invasive disease, patient selection for surgery, radiation therapy, choice of adjuvant endocrine therapy, and the potential role for neoadjuvant therapy have each become the subject of therapeutic trials in DCIS. Again as a parallel to invasive disease, locoregional control and event-free survival in the context of the morbidities of radiation therapy and drug therapies require consideration. There are now trials underway to address the question of overtreatment and determine whether nonsurgical management of low-risk (for progression) DCIS can be managed by medical therapy alone.

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SURGICAL MANAGEMENT

The current gold standard for surgical treatment of DCIS is excision to negative margins. Lumpectomy (segmental or partial mastectomy) with radiation or mastectomy represents guideline-concordant care for DCIS as outlined by the National Comprehensive Cancer Network (NCCN) treatment recommendations.[1] These guidelines are based on the findings of equivalent survival outcomes for patients with invasive breast cancer shown for both surgical approaches in randomized clinical trials.[2,3] The decision between breast conservation and mastectomy for DCIS is based on clinical, pathologic, and patient-related factors. DCIS is most commonly identified as a unifocal, nonpalpable lesion identified on mammography. Localization with a radioactive seed or wire is often necessary to facilitate breast conservation therapy (BCT). Multifocality, large-volume disease (with inability to obtain negative margins), or inability to obtain a favorable cosmetic outcome (even with oncoplastic techniques) may drive surgical decision making toward mastectomy. Although a nipple-sparing mastectomy may be appropriate for patients with early-stage, biologically favorable invasive cancers that are node negative and located in the periphery of the breast,[4] greater caution may be required for patients with DCIS. Extensive, centrally located, and subareolar DCIS less than 2 cm from the nipple areolar complex may be considered contraindications to a nipple-sparing approach. Contralateral prophylactic mastectomy incurs no survival benefit in patients who do not have a genetic predisposition for the development of invasive breast cancer[5] and thus should also be viewed with caution for individuals with DCIS.

When a mastectomy is planned for a diagnosis of DCIS, sentinel lymph node (SLN) biopsy should be considered, given the difficulty of axillary lymph node mapping if invasion is identified on final pathology after the breast has been removed. SLN biopsy alone carries a risk of wound infection, seroma, lymphedema, and pain/paresthesias, although lower than that associated with axillary lymph node dissection.[6] Hence, most clinicians caution that SLN biopsy for DCIS in BCT should not be routine[7–9] but considered at the time of completion mastectomy for positive/close margins following BCT (and attempted reexcision).[10]

RADIATION THERAPY

Women with DCIS who undergo breast-conserving surgery receive adjuvant radiotherapy in up to two-thirds of cases in published series. In contrast with invasive breast cancer, radiation therapy is rarely used following mastectomy for DCIS. Whole-breast radiotherapy following breast-conserving surgery reduces local recurrence (DCIS and invasive breast cancer) from 28.1% to 12.9% and reduces the incidence of invasive disease from 11.0% to 5.0% at 10 years as reported in a meta-analysis[11] based on key trials including the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-17, NSABP B-24,[12] and the United Kingdom/Australia and New Zealand[13] (United Kingdom/ANZ) DCIS trials.

Although the extent of margin of clearance around DCIS has been hotly debated over the years, it is probable that at least a negative margin is required for the beneficial effects of breast radiotherapy to be realized. The dose and fractionation regimens for whole-breast radiotherapy for DCIS after breast-conserving surgery mirror practices for invasive disease, with a trend toward the use of hypofractionation and the potential added value of a boost to the tumor (DCIS) bed.[14] Whether alternative approaches to whole-breast irradiation to the DCIS resection bed (eg, using intracavity radiotherapy techniques) are equivalent to external beam radiation therapy is currently unclear and the subject of clinical trials. The side effects, such as skin

toxicity and potential cardiac effects, as for invasive breast cancer, need to be considered with each approach. Although radiation therapy reduces in-breast recurrence by half (DCIS and invasive breast cancer), use of radiation therapy does not seem to alter long-term breast cancer–specific survival for patients diagnosed with pure DCIS.[11] There may be less benefit for radiation therapy following BCT for DCIS in the elderly population, similar to invasive disease. Although avoidance of radiation is associated with increased risk for locoregional recurrence, omission of radiation therapy may be a viable option for elderly patients with hormone receptor–positive disease receiving endocrine therapy, because such a strategy does not lead to decreased disease-free or overall survival.[15,16]

The Oncotype DX DCIS Score is a 12-gene assay that provides individualized 10-year risk of locoregional recurrence (in situ and invasive disease) following treatment with breast-conserving surgery alone.[17] The DCIS Score has been validated in different patient populations as an independent predictor of recurrence risk beyond clinical and pathologic variables and may support the omission of radiation therapy in some patients with low risk of recurrence.[18] The rigid eligibility criteria for the landmark validation study E5194 (25 mm maximum size for low-grade/intermediate-grade DCIS, 10 mm for high-grade DCIS, and 3-mm resection margins) and the historically high recurrence rates should be considered. Although clinical application of the DCIS score is not standard of care, it may inform clinicians and patients as to the likely benefits of adjuvant therapy.

ENDOCRINE THERAPY

The value of adjuvant endocrine therapy to prevent further DCIS or subsequent invasive breast cancer following resection of estrogen receptor (ER)–positive DCIS has followed the evidence in favor of such an approach for ER-positive invasive breast cancer but remains controversial. Not every DCIS is universally examined for ER (or HER2) status. There is a need not simply to show evidence of efficacy of endocrine therapy to reduce in-breast recurrence but also to recognize the potential to prevent contralateral and distant breast events balanced against the side effects of, and adherence to, endocrine therapy.

The NSABP B-24 trial found that in premenopausal and postmenopausal patients treated for DCIS with lumpectomy and adjuvant radiation therapy, tamoxifen reduced the risk of ipsilateral local recurrence by 30% and for contralateral breast cancer by 50%.[19] The absolute risk at 5 years of any (invasive or noninvasive) breast cancer event was small (tamoxifen arm 8% and placebo arm 13%) and survival was not influenced by treatment. A more complex trial design in the United Kingdom/ANZ DCIS trial (2 $\times$ 2 trial of tamoxifen vs radiation therapy) examined the use of tamoxifen versus no adjuvant therapy following complete local excision of DCIS in the presence or absence of radiation therapy.[13] The trial results suggested that, in the absence of radiation therapy, tamoxifen was associated with a 30% overall reduction in breast cancer events through reduction in DCIS recurrence, contralateral DCIS, and invasive disease events. However, tamoxifen was ineffective in preventing ipsilateral invasive recurrence and, in the presence of radiation therapy, tamoxifen had no added benefit. Survival was not affected by radiation therapy or tamoxifen in the United Kingdom/ANZ DCIS trial, with breast cancer accounting for only 20% of all deaths.[13] A meta-analysis including these 2 key trials suggests modest additional benefit of tamoxifen compared with a combination of breast-conserving surgery and radiation therapy for local recurrence, with a reduction from 14.1% to 9.7%.

Recently, the aromatase inhibitor anastrozole has been compared with tamoxifen in 2 large randomized trials enrolling postmenopausal women with DCIS. In NSABP B-35, which enrolled 3104 postmenopausal women who had undergone lumpectomy to clear margins and adjuvant radiation for DCIS, anastrozole treatment was associated with a small but statistically significant improvement in breast cancer–free interval compared with tamoxifen (hazard ratio [HR], 0.73; 95% confidence interval [CI], 0.56–0.96; $P = .023$), although disease-free survival was the same at 120 months (HR, 0.89; 95% CI, 0.75–1.07; $P = .21$).[20] Among postmenopausal women less than 60 years old (n = 1447), anastrozole was associated with significant improvements in breast cancer–free interval and disease-free survival compared with tamoxifen (HR, 0.53; 95% CI, 0.35–.080; and HR, 0.69; 95% CI, 0.51–0.93, respectively). However, the International Breast Intervention Study (IBIS) II trial, which enrolled 2980 postmenopausal women with DCIS who had undergone lumpectomy to clear margins with or without radiation, failed to show an improvement with anastrozole compared with tamoxifen (HR, 0.89; 95% CI, 0.64–1.23; $P = .49$).

The reduction in contralateral cancer and possibly local recurrence of DCIS with endocrine therapy needs to be weighed against the potential side effects of tamoxifen (hot flashes, deep vein thrombosis, or endometrial cancer) and aromatase inhibition (hot flashes, arthralgias, osteopenia, or osteoporosis). The impact on quality of life of endocrine therapy side effects and other diseases associated with these agents gives pause for thought. In addition, the issue of adherence is important with endocrine therapy, in which only 70% of women in the IBIS II[21] trial were still taking their endocrine agents at 5 years. If extrapolated to the wider community, this finding could diminish the value of adjuvant endocrine therapy for DCIS.

NEOADJUVANT THERAPY

Neoadjuvant therapy has become standard of care for advanced breast cancer and an option for reducing the size of the primary tumor in patients with early-stage invasive breast cancer (and hence facilitating breast conservation rather than mastectomy as a surgical option). However, there is currently little evidence in favor of the neoadjuvant approach for treatment of DCIS. For ER-positive DCIS, targeting the ER preoperatively has been the focus of the Cancer and Leukemia Group B (CALGB) 40903 trial. Patients receive 6 months of neoadjuvant letrozole before surgical intervention. There have been several trials targeting HER2-positive DCIS, with HER2 targeting agents including trastuzumab[22] and lapatinib.[23] The neoadjuvant approaches are largely used to further understand the biology of DCIS. If there is a clinical need to defer conventional surgical intervention for DCIS, such drug-based therapeutic approaches may be a useful option.

Thus, the standard approaches to managing DCIS have largely been derived and followed on from the treatment of invasive disease, despite the probability that most women diagnosed with DCIS will not die from breast cancer.[24] Hence, considered approaches to DCIS that reflect the concerns regarding overtreatment and the different outlook to invasive breast cancers have recently been developed.

MEDICAL THERAPY ALONE

Although surgical resection has been standard practice for DCIS, a small proportion of women in the United States (~1.5%) decline surgery and opt for medical intervention alone. Recent prospective, population-based data suggest that segmental mastectomy or modified radical mastectomy may be associated with surprisingly high levels of chronic pain, disability, and psychological distress, often resistant to management,

4 and 9 months after breast surgery.[25] Taken together with the exceptional long-term survival rates for women with DCIS, this has led some clinicians to question the need for surgical intervention.

However, DCIS (like invasive breast cancer) shows a spectrum of phenotypic behaviors ranging from indolence through progression to invasive disease. Thus, for nonsurgical management of DCIS, targeting low-risk (for progression) DCIS as the focus for medical management alone is most attractive, reflecting similar strategies implemented for selected patients with prostate and thyroid neoplasms. Internationally, there are 3 clinical trials (**Fig. 1**) designed to determine the effect of nonsurgical management of low-risk DCIS: the Comparison of Operative to Monitoring and Endocrine Therapy (COMET[26]) trial in the United States, the Low-risk DCIS (LORIS[27]) trial in the United Kingdom, and the Management of Low-grade DCIS (LORD[28]) trial in Europe. A fourth trial, the Low and Intermediate-risk Ductal Carcinoma Study, has been proposed in Australia and New Zealand. Although the LORIS trial has already shown the feasibility of randomizing patients between surgical and nonsurgical management, the US-based Comparison of Operative to Monitoring and Endocrine Therapy (COMET) trial merits particular attention. COMET, sponsored by the Alliance for Clinical Trials in Oncology, will not only randomize patients between guideline-concordant care (surgery, with or without radiation therapy and/or endocrine therapy) versus active surveillance (with the option of endocrine therapy) but will also monitor outcomes in those not participating in the trial. The identification of subsequent invasive breast cancer is the primary outcome; however, patient-reported outcomes and other breast and health outcome measures will also be captured. There are subtle differences between the 3 currently recruiting trials (COMET, LORIS, LORD) in terms of patient characteristics, imaging, and pathology features, and also some differences between the active surveillance arms (mammographic surveillance every 6 months in COMET but every 12 months in LORIS and LORD) (**Table 1**). However, the intent is for the 3 trials to ultimately allow for meta-analysis in order to provide high-level guidance regarding management options for patients with DCIS.

CONTROVERSIES FOR NONSURGICAL APPROACHES

Before guideline-concordant care or active surveillance, there is clearly a need to image and establish the diagnosis based on sufficient sampling of the lesion using core needle biopsies (**Fig. 2**). A legitimate concern for the conservative management of clinically low-risk DCIS (active surveillance, endocrine therapy, observation alone) is the failure to identify the presence of invasive carcinoma at the time of diagnosis. A meta-analysis examining 7350 cases of DCIS identified by core needle biopsy found invasive cancer at excision in 1736, thus underestimating the disease in 25.9% of cases.[29] More recent data from a national screening program with quality assurance measures in place for imaging and pathology suggest that the figure may still be around 20%.[30] Predictive variables associated with underestimating invasive disease include the presence of a palpable lesion, mammographic mass, the use of a smaller-gauge biopsy device (14 vs 11 gauge), and higher BIRADS (Breast Imaging Reporting and Data System) categorization. Subsequent studies evaluating upgrade rates further identified seemingly cumulative risk factors[31] and have led to the creation of predictive nomograms.[32,33]

To evaluate the safety of observation in DCIS, Pilewskie and colleagues[34] identified a cohort of 296 patients who met some of the eligibility criteria for the LORIS trial. Most patients (82%) had intermediate-grade DCIS on core biopsy, and more than half (62%) of the core biopsies in the study were performed with a vacuum-assisted 8-gauge or

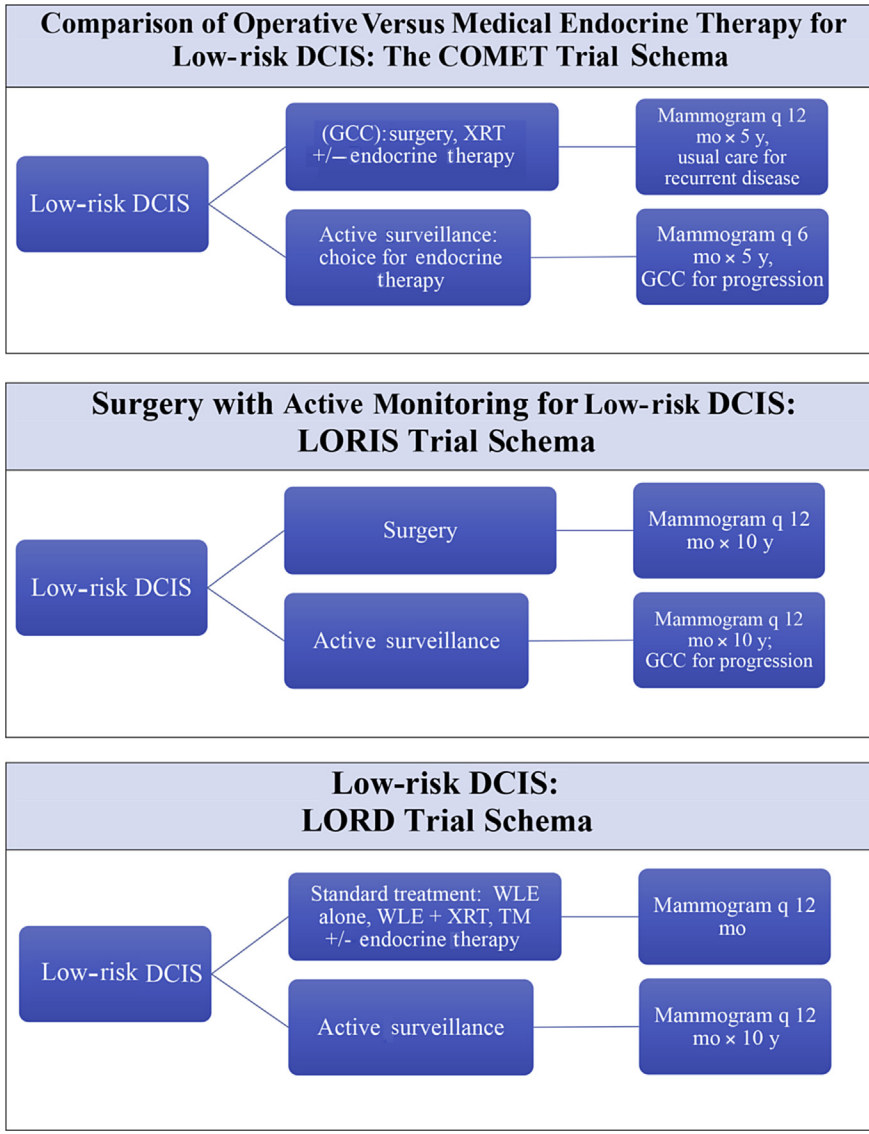


Fig. 1. Comparison of the COMET (Comparison of Operative to Monitoring and Endocrine Therapy), LORIS (Low-risk DCIS) and LORD (Management of Low-grade DCIS) trials. GCC, guideline-concordant care; q, every; TM, total mastectomy; WLE, wide local excision; XRT, external radiation therapy.

9-gauge core needle. Although this retrospective review did not mirror LORIS precisely, 20% of patients in this single-center retrospective review were found to have invasive carcinoma on final pathology. Intermediate-grade DCIS was a statistically significant factor; 23% of patients with intermediate-grade DCIS were upgraded based on final pathology compared with only 7% in those with low-grade DCIS. More recently, Grimm and colleagues[35] identified a contemporary cohort of patients diagnosed with DCIS by vacuum-assisted core biopsy (n = 307), some of whom

Table 1
Comparison of active surveillance trials in ductal carcinoma in situ

	COMET	LORIS	LORD
Patient characteristics			
Age (y)	≥40	≥46	≥45
History of other cancer	NA	INCLUDE	EXCLUDE with exceptions[a]
History of breast cancer	EXCLUDE	EXCLUDE	NA
Synchronous iInvasive cancer	EXCLUDE	EXCLUDE	EXCLUDE
Bilateral DCIS	INCLUDE	INCLUDE	EXCLUDE
Prior chemoprevention	EXCLUDE	NA	NA
High risk	INCLUDE	EXCLUDE[b]	EXCLUDE if BRCA mutation
Symptomatic	EXCLUDE	EXCLUDE	EXCLUDE
Imaging characteristics			
Morphology	Calcifications only	Calcifications only	Calcifications only
BIRADS	≤3	NA	NA
Size	NA	NA	Any
Biopsy technique	VACB or surgical	VACB or surgical	VACB
Device Gauge, # of cores	NA, NA	≤12 G, NA	8–9 G, 6 cores or 10–11G, 12 cores
Pathologic features			
Nuclear grade	Low and intermediate	Low and intermediate	Low
Hormone receptor	ER+ or PR+, HER2−	NA	NA
Comedonecrosis	EXCLUDE	EXCLUDE	NA
Key differences	Active surveillance arm: mammography q 6 mo × 5 y Two local pathologists to agree pathologic features	Active surveillance arm: mammography q 12 mo × 10 y Requires central pathology review before randomization	Active surveillance arm: mammography q 12 mo × 10 y
Outcome measures			
Primary	New ipsilateral invasive cancer in GCC and AS arms at 2 y	Ipsilateral invasive breast cancer–free survival time	Ipsilateral invasive breast cancer–free rate at 10 y
Secondary	QOL, psychological outcomes, rate of surgery, overall survival	Time to ipsilateral or contralateral invasive breast cancer, time to surgery, QOL, cost	Time to ipsilateral grade II–III DCIS, contralateral DCIS, contralateral invasive breast cancer, distant metastasis–free and overall survival

Abbreviations: AS, active surveillance; BIRADS, Breast Imaging Reporting and Data System; G, gauge; GCC, guideline-concordant care; NA, not applicable; q, every; QOL, quality of life; VACB, vacuum assisted core biopsy.

[a] Exceptions include in situ cancer of the cervix and basal carcinoma of the skin.

[b] If high risk per United Kingdom NICE (National Institute for Health and Care Excellence) guidelines.

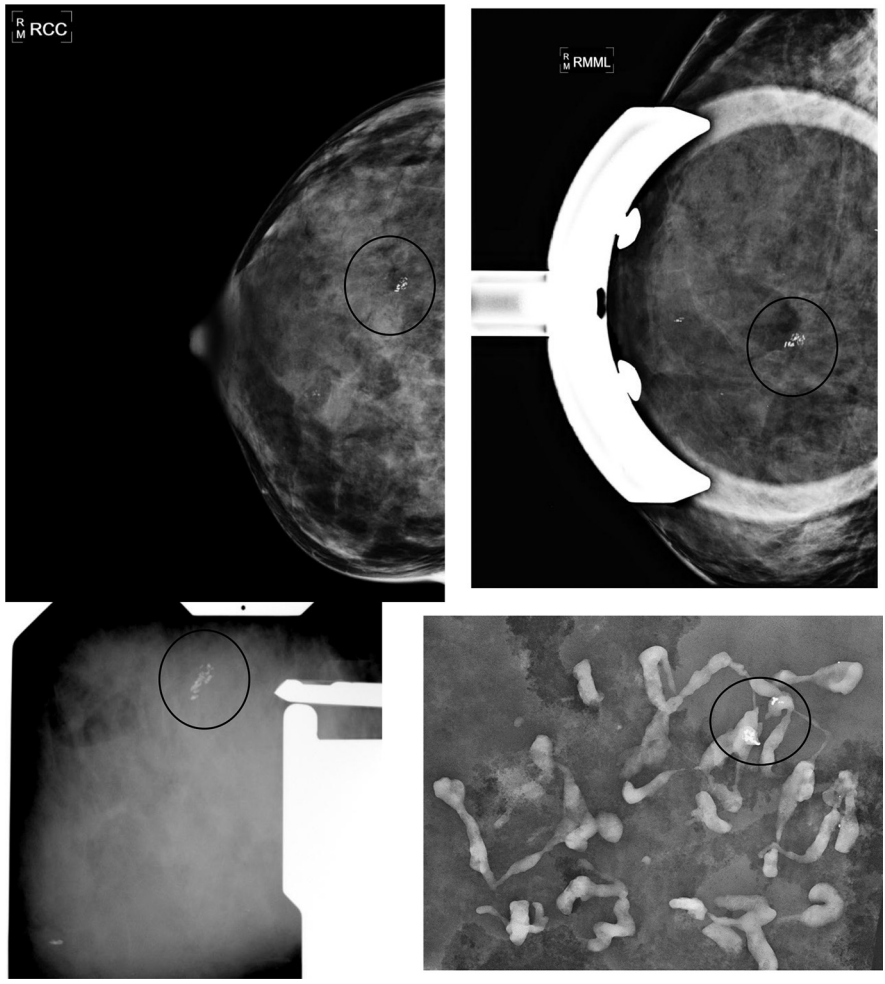


Fig. 2. Example of a low-risk lesion on mammogram (*upper right*) and magnification view (*upper left*) with stereotactic targeting (*lower left*) and multiple cores (*lower right*) containing microcalcifications (*circled*).

(n = 81) met the eligibility criteria for the active surveillance trials (COMET, LORIS, and LORD). The overall upgrade rate to invasive disease was 17% (53 of 307). However, upstage rates in patients who met trial inclusion criteria were more reassuringly 6% for COMET, 7% for LORIS, and 10% for LORD. All upstaged cases were node negative, hormone receptor positive (ER, PR), and HER2 nonamplified, indicating a traditionally very favorable subset in terms of long-term survival and provided strong reassurance that, using the current trials criteria, any potential for missed upgraded (invasive) lesions would likely not affect patient survival.

PATIENT-REPORTED OUTCOME MEASURES

A multitude of psychological, social, and physical stresses accompany the diagnosis and subsequent treatment of DCIS or invasive breast cancer. Anxiety, depression, fear

of recurrence, pain, fatigue, body image issues, and sexual dysfunction have been found to affect quality of life and even long-term overall survival in patients with invasive breast cancer.[36–38] A recent meta-analysis of patient-reported outcomes identified that these treatment-associated physical, mental, and sexual health issues also pertain to women with a diagnosis of DCIS.[39]

In those women who undergo surgical management of DCIS, there is a risk of developing chronic pain at the surgical sites.[25] Persistent pain after lumpectomy may be as prevalent as pain after total mastectomy, leading to both physical and psychological disability, which is often resistant to management. One prospective study identified patient-specific and surgery-specific risk factors for postoperative pain, and showed remarkably high levels of chronic pain 4 and 9 months after breast surgery.[40] Prospective randomized trials designed to identify low-risk DCIS that can be safely managed with active surveillance may allow some women to safely avoid surgery and the associated complications.

SUMMARY

The contemporary understanding of the heterogeneous nature of DCIS has led to less invasive treatment in selected patients with low-risk disease and suggestions that the word carcinoma may not be appropriate in this diagnosis. A working group from the National Cancer Institute suggested that the word cancer to describe premalignant conditions such as DCIS should no longer be used, because this term almost mandates more aggressive treatment to halt otherwise definite progression to a lethal disease process.[41] Advocates of the name change call on studies linking patient anxiety and distress to overestimation of breast cancer risk.[42,43]

Treatment of DCIS, including surgery, radiation, and/or drug therapies, has largely followed the lead of invasive breast cancer. Although some benefit has been seen for the use of radiation therapy and/or endocrine agents in reducing locoregional events, without any impact on survival, the value of nonsurgical therapies (radiotherapy and endocrine therapy) for DCIS is less certain than for invasive breast cancer. However, trials around the world are seeking to determine whether DCIS at low risk for progression may be managed without surgical intervention, relying on medical therapy to control breast neoplasia reflecting the indolent process of DCIS in selected patients. In addition, alternative strategies, such as vaccinations and harnessing the immune system, are currently being investigated.[44,45] These strategies could offer promising insights and novel treatment approaches to appropriately selected women. A key to determining how best to manage DCIS in the future is the global activity of randomized clinical trials now underway, which are likely to take 5 to 10 years to produce clinically actionable data. In the meantime, appropriately selected patients should be offered entry into these trials to address this pressing question: are there alternative strategies to surgery for selected women in the management of DCIS?

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