Ductal Carcinoma In Situ of the Breast: Can Biomarkers Improve Current Management?

John M.S. Bartlett,1* Sharon Nofech-Moses,2 and Eileen Rakovitch2

BACKGROUND: Screening for invasive cancer has led to a marked increase in the detection of ductal carcinoma in situ (DCIS). DCIS is, if appropriately managed, a low-risk disease which has a small chance of impacting on patient life expectancy. However, despite significant advances in prognostic marker development in invasive breast cancer, there are no validated diagnostic assays to inform treatment choice for women with DCIS. Therefore we are unable to target effective treatment strategies to women at high risk and avoid overtreatment of women at low risk of progression to invasive breast cancer. Paradoxically, one effect of this uncertainty is undertreatment of some women.

CONTENT: We review current practice and research in the field to identify key challenges in the management of DCIS. The impact of clinical research, particularly on the over and undertreatment of women with DCIS is assessed. We note slow progress toward development of diagnostic biomarkers and highlight key opportunities to accelerate advances in this area.

SUMMARY: DCIS is a low-risk disease, its incidence is increasing, and current treatment is effective. However, many women are either over- or undertreated. Despite repeated calls for development of diagnostic biomarkers, progress in this area has been slow, reflecting a relative lack of investment of research effort and funding. Given the low event rate in treated patients and the lateness of recurrences, many previous studies have only limited power to identify independent prognostic and predictive biomarkers. However, the potential for such biomarkers to personalize treatment for DCIS is extremely high.

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Background: DCIS, the Current Clinical Challenge

Epidemiology of DCIS

Ductal carcinoma in situ (DCIS)3 of the breast is a non-obligate precursor of invasive carcinoma which, by definition, involves proliferation of abnormal epithelial cells limited by the basement membrane of the breast ductal system without stromal invasion. The widespread adoption of screening mammography, to improve early detection of invasive breast carcinomas, over the past 2–3 decades has led to a significant increase in the incidence of ductal carcinoma in situ (DCIS) of the breast (1, 2). DCIS now accounts for about 20%–25% of all newly diagnosed cases of breast cancer in the US and 17%–34% of cases detected by mammographic screening (3, 4). Approximately 1 in every 1300 mammography examinations performed will lead ultimately to a diagnosis of DCIS (1). During 25 years of screening, the incidence of invasive breast cancer has continued to increase (5), and screening for invasive breast cancer, in line with screening for colon and cervical cancer, is thought to lead to earlier detection and improved outcomes. In contrast, the markedly increased detection and treatment of DCIS, incidental to screening for invasive cancers, has not led to a clear reduction in the incidence of invasive breast cancer following DCIS (5). Mortality from breast cancer following a diagnosis of DCIS is very low regardless of the type of treatment women undergo. Only 1%–2.6% of women diagnosed with DCIS will die of invasive breast cancer within 8–10 years of the primary diagnosis (6–8). Thus 1 sequela of breast screening programs worldwide has been a marked increase in the over-detection and overtreatment of DCIS.

Natural History of DCIS

The natural history of untreated DCIS remains unknown because most individuals diagnosed with DCIS are treated by surgical excision. The most informative

1 Ontario Institute for Cancer Research, Toronto, ON, Canada; 2 Sunnybrook Odette Cancer Centre, Toronto, ON, Canada.

* Address correspondence to this author at: Transformative Pathology, Ontario Institute for Cancer Research, MaRS Centre, South Tower, 101 College St., Suite 800, Toronto, Ontario, Canada M5G 0A3. E-mail: john.bartlett@oicr.on.ca.

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3 Nonstandard abbreviations: DCIS, ductal carcinoma in situ; NSABP, National Surgical Adjuvant Breast Project; ER, estrogen receptor; PgR, progesterone receptor; HER2, human epidermal growth factor receptor homolog 2; XRT, radiation; BCS, breast-conserving surgery; CNA, copy number alteration; IHC, immunohistochemistry; COX-2, cyclooxygenase 2; FISH, fluorescence in situ hybridization.
data are from 3 small retrospective case series of women who underwent excisional biopsy of presumed benign breast lesions and who, on retrospective pathology review, were discovered to have DCIS. These small studies reported that 11%–32% of patients developed an invasive carcinoma within the same breast 17.5–25 years after diagnosis, suggesting that in some cases inadequately excised DCIS may progress to invasive cancer (6, 9–11). It remains unclear to what extent these findings can be applied to women with mammographically detected DCIS, which comprise the majority of cases of DCIS diagnosed today. However, these data suggest that whereas some women with DCIS will develop invasive breast cancer, the majority of women with DCIS, if left untreated, are not destined to recur let alone die of their disease. However, our current inability to predict which women diagnosed with primary DCIS will subsequently progress to invasive cancer results in almost all women diagnosed with DCIS undergoing some form of surgical treatment and/or adjuvant treatment.

PRESENTATION OF DCIS
Most women (80%–85%) diagnosed with DCIS present with a mammographic abnormality (usually pleomorphic calcifications) in the absence of clinical symptoms. About 15%–20% of cases present with clinical symptoms including breast lump, nipple bleeding/discharge, or Paget disease. About 96% of DCIS lesions diagnosed on mammography are detected by performing a biopsy of areas of the breast containing detectable calcifications (3, 4).

PATHOLOGICAL ASSESSMENT OF DCIS
Accurate pathologic assessment of DCIS is critical, to exclude the presence of invasive cancer and determine the most appropriate treatment. Given the markedly higher risk of metastasis and death among women diagnosed with invasive breast cancer (compared with DCIS), additional treatment such as chemotherapy or hormonal therapy is usually recommended (6). Therefore, the misclassification of invasive breast cancer as DCIS, or vice versa, has profound prognostic and therapeutic implications. Misclassification may result from either sampling or interpretation errors. Variations in tissue handling, grossing protocols, and extent of sampling of blocks for microscopic evaluation continue to pose a challenge for practicing pathologists evaluating resection samples for DCIS. One key limitation in excluding invasive foci in cases of DCIS is the reliance on tissue sampling. The College of American Pathologists currently recommends microscopic examination, when practical, of the entire imaging abnormality in nonpalpable lesions as well as all areas of gross lesion identified (12). It is currently impractical to entirely submit large lumpectomies or mastectomies for such extensive microscopic evaluation, and even when the entire radiologic and gross abnormalities are sampled, only one 5-μm section is reviewed from each 2- to 3-mm-thick tissue sample embedded in paraffin blocks.

Assessment of extent of DCIS and distance to clear margins is strongly dependent on the method of sampling. Samples are grossed and sampled on the basis of the presence of a palpable macroscopic lesion and pre-surgical breast imaging. Nonpalpable lesions, require radiography of the excised sample—radiography either by placing the whole sample on a grid or radiography of serially sliced samples. Visible or palpable lesions can be sampled to include the entire abnormality and sections examined to demonstrate the relationship to the margins. According to the National Surgical Adjuvant Breast Project (NSABP) B17 protocol, 80% of DCIS cases were nonpalpable (13). In such cases, the size may be determined by radiology, but this method may significantly underestimate the size in 23% (14). The sensitivity of estimation of extent of DCIS is lower for nonpalpable lesions (15), whereas accuracy of determining microinvasion by use of various grossing techniques is currently unknown.

Stromal invasion, defined as presence of malignant cells beyond the basement membrane, is usually recognized on routine staining as individual cells or irregular nests arranged haphazardly in the stroma. In difficult cases, immunohistochemistry is helpful to demonstrate absence of myoepithelial cells by use of 1 or more myoepithelial cell markers (the most commonly used are smooth muscle myosin, p63, and calponin). Overdiagnosis of invasion may occur when malignant cells are displaced to the stroma by core needle biopsy, and therefore stromal invasion should not be determined in an area of linear fibrosis, fat necrosis, and hemosiderin deposits, features characteristic of a needle tract. Other reasons for overcalling stromal invasion may be related to tangential cutting, cancrization of lobules, and involvement of sclerosing adenosis or a radial scar (16). Interpretational errors include overdiagnosis of benign lesions as DCIS (for example, florid usual hyperplasia) or underdiagnosis of invasive carcinoma (for example, when microinvasion is overlooked or when invasive cribriform carcinoma is not recognized). A central pathology review of samples obtained from the 2 randomized trials resulted in the reclassification of 9% of lesions diagnosed as DCIS, with 7% reclassified as benign disease and 2% as invasive cancer (17, 18). The pathology review of the European Organization for Research and Treatment of Cancer trial identified 45 cases of invasive cancer misdiagnosed as DCIS. Nine percent of these women (4 of 45) developed an invasive recurrence (17). These findings have
resulted in practice guidelines that include a recommendation that all DCIS samples be reviewed by a pathologist with expertise in breast disease (19, 20).

Pathologic assessment of DCIS is focused on determining the extent of disease and margin status, both parameters that have been shown to be associated with local recurrence (21) as well as grade and presence of comedo necrosis, variables that are currently taken into consideration when adjuvant treatment is considered (22). Unless hormonal therapy is indicated (see below) immunohistochemical measurement of conventional breast markers such as estrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor receptor homolog 2 (HER2) is of limited value in DCIS.

### TREATMENT OF DCIS

Before the 1980s, DCIS was rare, and the most common presentations were a palpable mass, nipple discharge, or Paget disease. Treatment for these symptomatic DCIS lesions was mastectomy because DCIS was frequently distributed throughout the entire breast and there were concerns that any residual DCIS in the breast might progress to invasive cancer. Mastectomy provides excellent local control with minimal rates of recurrence (<5% at 10 years) but may be associated with reduced body image and quality of life (23, 24).

The advent of screening, as noted above, has increased incidence of DCIS dramatically. Furthermore, past studies report that DCIS that presents with frank symptoms, such as palpable mass, nipple discharge, or Paget disease, may have a higher risk of recurrence in comparison with DCIS detected by screening mammography in otherwise asymptomatic individuals (8).

The implementation of screening mammography has been associated with a substantial decrease in the average size of DCIS lesions at presentation, from 60 to 10 mm, such that the majority of DCIS tumors now diagnosed are considered amenable to complete excision without mastectomy (25). Randomized controlled trials have established that lumpectomy plus radiation leads to equivalent survival vs mastectomy for the treatment of early breast cancer (26). Therefore most DCIS detected in the current era of screening mammography will be able to be completely excised without removal of the entire breast, resulting in good cosmesis and low recurrence rates (27, 28).

### Randomized controlled trials comparing lumpectomy to lumpectomy and XRT as treatment for DCIS

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>Median follow-up, years</th>
<th>Negative margins, %</th>
<th>Local recurrence rate</th>
<th>Invasive local recurrence rate</th>
<th>Breast cancer mortality</th>
<th>Overall mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B-17 [Wapnir et al. (34)]</td>
<td>818</td>
<td>17.3</td>
<td>87</td>
<td>35 vs 19.5 0.49 19 vs 9</td>
<td>0.48 3 vs 5</td>
<td>1.44 16 vs 17</td>
<td>1.08</td>
</tr>
<tr>
<td>EORTC 10853 [Bijker et al. (45)]</td>
<td>1010</td>
<td>10.5</td>
<td>84</td>
<td>26 vs 14 0.52 13 vs 8</td>
<td>0.58 3 vs 3.4</td>
<td>5 vs 5</td>
<td></td>
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<tr>
<td>SweDCIS [Emdin et al. (71)]</td>
<td>1067</td>
<td>8</td>
<td>80</td>
<td>26 vs 11.5 0.41 12 vs 7</td>
<td>0.6 vs 0.2</td>
<td>9.6 vs 8.4</td>
<td></td>
</tr>
<tr>
<td>UK/ANZ [Cuzick et al. (33)]</td>
<td>1030</td>
<td>12.7</td>
<td>100</td>
<td>14 vs 6 0.41 10 vs 5.6</td>
<td>0.32 2.7 vs 1.5</td>
<td>9.9 vs 11.8</td>
<td></td>
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<tr>
<td>EBCCTG [Correa et al. (31)]</td>
<td>3729</td>
<td>8.9</td>
<td>89</td>
<td>28.1 vs 12.9 0.46 11 vs 5</td>
<td>NE 3.7 vs 4.1</td>
<td>1.22 8.2 vs 8.4</td>
<td></td>
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</table>

*HR, hazard ratio; EORTC, European Organisation for Research and Treatment of Cancer; SweDCIS, radiotherapy after sector resection for ductal carcinoma in situ of the breast; UK/ANZ, UK, Australia, and New Zealand; EBCCTG, Early Breast Cancer Trialists' Collaborative Group; NE, not estimated.

b P < 0.001.
c Not significant.
d P < 0.05.
e P < 0.0001.
f P < 0.00001.
ADJUVANT TAMOXIFEN AND OTHER ENDOCRINE THERAPIES

Despite the finding from 2 randomized controlled trials that adjuvant tamoxifen following BCS for DCIS decreases significantly the number of ipsilateral and contralateral breast cancer recurrences (33, 34), the use of tamoxifen in this setting remains controversial because of concerns related to toxicities such as an increased risk of thromboembolic events and endometrial cancer. Few guidelines provide clear recommendations on endocrine therapy for DCIS. Neither the NSABP B-24 nor the UK, Australia, and New Zealand studies showed any increase in other causes of mortality with the use of tamoxifen (33, 34). A subgroup analysis from the NSABP B-24 study has shown that the benefit of tamoxifen seems to be limited to ER⁺ DCIS. The National Comprehensive Cancer Network Guidelines (version 2.2011) recommend the use of 5 years of tamoxifen after BCS as a category I recommendation, especially for immunohistochemically ER⁺ DCIS (Table 2).

BCS WITHOUT ADJUVANT THERAPY

Despite the proven efficacy of radiotherapy and guideline recommendations, surveys of current clinical practice suggest half of women treated by local excision for DCIS do not receive radiation (35, 36). In the Surveillance, Epidemiology and End Results database, a survey of treatments offered to women diagnosed with DCIS in the US suggested that 46% of women treated by BCS did not receive radiation therapy (36–38). The reasons for the omission of radiotherapy are unclear but may be influenced by published reports of low rates of local recurrence in selected women with DCIS treated by BCS alone (without radiotherapy) (36, 39, 40). The Eastern Cooperative Oncology Group studied women with low risk DCIS who were treated by BCS alone (39). Women included in this study had high-grade DCIS ≤1 cm or low or intermediate nuclear grade <2.5 cm and a minimum negative resection margin width of 3 mm. After a median follow-up interval of 6 years, the rate of local recurrence was 10.5% (39). The Radiation Therapy Oncology Group 98–04 clinical trial randomized women with low-risk DCIS to receive radiation or observation; 62% received tamoxifen. At 5 years, the addition of radiation led to a significantly lower rate of local recurrence, 0.4% for women who received radiation vs 3.2% for those who did not (hazard ratio 0.14, 95% CI 0.03–0.61, \( P = 0.002 \)) (41). However, even without radiotherapy, in this group almost 97% of women did not experience relapse within 5 years.

Studies reporting low rates of recurrence following BCS alone are based on institutional case series or cohort studies of highly selected patients (e.g., small tumors, low/intermediate grade, and wide negative resection margins). More comprehensive, population-based studies suggest that local recurrence rates following BCS alone are higher than those achieved in highly selected cohort studies (42, 35). In 1 population-based study of 1036 women treated by BCS alone, 20% developed a local recurrence after a median follow-up interval of 78 months (8). In another population-based study of 460 women treated by BCS alone, 18% developed local recurrence after a median follow-up of 9.4 years (43, 44). These data suggest that treatment by BCS alone is offered to individuals with higher risk DCIS than those entered into the clinical trials, which resulted in higher rates of recurrent breast cancer that might have been avoided with treatment.

The above data suggest that individuals with high-grade DCIS are not good candidates for treatment by
BCS alone. Individuals with high grade DCIS who develop a local recurrence have an increased risk of developing subsequent distant metastases (45). Nevertheless, population studies report that one third of women with high-grade DCIS, treated by BCS, do not receive radiation treatment. In our population study, we found that 22% of all women with high-grade DCIS treated by BCS alone (without XRT) and 29% of those with high-grade disease under the age of 50 years developed a subsequent local recurrence (35, 36, 46).

It is not clear why radiotherapy is omitted in individual cases. Possible reasons include patient preference, access to therapy, and the physicians’ interpretation of the risks and benefits of radiotherapy. In some cases, the omission of radiation is due to suboptimal compliance with treatment guidelines.

Conversely, since it is challenging to identify a low-risk group on the basis of clinical and pathological grounds alone, many women receive unnecessary radiation treatment. Fourteen patients require radiotherapy to prevent 1 local recurrence, and 25 would need to be treated to prevent 1 mastectomy (46). Additional population-based data are needed to evaluate the long-term toxicities of radiotherapy and determine the impact of radiation on long-term breast preservation and breast cancer mortality. Focusing radiotherapy toward those women at high risk of relapse, if they could be prospectively identified, would reduce overtreatment of women with DCIS, reduce the burden of breast cancer, and improve compliance with treatment guidelines.

CLINICAL, PATHOLOGICAL, AND MOLECULAR PREDICTORS OF RECURRENCE FOR DCIS

There are several candidate diagnostic markers for detecting recurrence following DCIS but, to date, none has shown value in specifically detecting invasive recurrence risk. However, the need for such markers is paramount, since a reduction in breast screening programs is not regarded as likely in the future and thus the reality is that there will be continued diagnosis of large numbers of cases of DCIS annually worldwide. The 2009 NIH State-of-the-Science Conference highlighted the need to develop and validate risk stratification models and in particular molecular methods for the diagnosis and management of DCIS: “The outcomes in women treated with available therapies are excellent. Thus, the primary question for future research must focus on the accurate identification of patient subsets diagnosed with DCIS, including those persons who may be managed with less therapeutic intervention without sacrificing the excellent outcomes presently achieved.”

Similarly, an exercise polling more than 170 international experts on research and treatment of breast cancer identified as the third most important matter for breast cancer research as, “Determine the factors in DCIS and/or atypical ductal hyperplasia which lead to progression into invasive carcinoma” (47, 48).

There is therefore a pressing need for novel diagnostic approaches to improve risk stratification of individuals with DCIS to allow improved targeting of effective treatments to those most likely to benefit.

Molecular Progression of DCIS—Through a Glass, Darkly

Cancers are the result of an accumulation of somatic mutations involving key growth, differentiation, and cell communication pathways (49, 50). Point mutations, copy number alterations (CNAs), epigenetic modifications, and general genome instability occur in nearly all tumor types studied and are frequently associated with disease progression (51).

There is limited information on the functional molecular events that drive progression of DCIS from the primary diagnosis of a pure noninvasive carcinoma in situ to a frankly invasive carcinoma. Reviews of the literature can be deceptive, since many studies fail to adequately distinguish DCIS with (or in the presence of) invasive carcinoma from cases of pure DCIS (i.e., DCIS in the absence of invasion). Clearly, from both a clinical and molecular perspective, these DCIS entities are likely to represent separate entities, and current evidence would appear to support this (52–54).

Evidence on the molecular characterization of pure DCIS is sparse, although the number of small molecular studies is growing. Data comparing molecular pathways in both primary DCIS and subsequent invasive breast cancers within the same patient is far more limited. Therefore it remains challenging and premature to build a comprehensive picture of the events involved in progression of pure DCIS to invasive cancer with any certainty.

Recent molecular studies of DCIS suggest 2 areas of controversy. The first is a debate relating to a simple linear multistep model of progression from DCIS to invasive breast cancer vs distinct pathways for low- vs high-grade invasive cancer developing from low- vs high-grade DCIS, respectively. The second relates to molecular differences observed between pure DCIS and DCIS with invasion. In this area, distinct molecular profiles are emerging which seem to suggest that pure DCIS (i.e., DCIS diagnosed with no evidence of invasive cancer in the breast) may be molecularly distinct from DCIS with invasion (i.e., DCIS that is present contemporaneously with invasive carcinoma).

The linear models of cancer progression hypothesize that premalignant stages occur sequentially in the development of invasive disease (55, 62). There is evi-
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Summary and Conclusion

As an unintended consequence, screening for invasive breast cancer has resulted in a marked increase in the diagnosis of asymptomatic ductal carcinoma in situ. The majority of women diagnosed with screen-detected DCIS are not destined to relapse or die of their disease. Clinical or pathological biomarkers that can reliably identify the subset of patients with DCIS at

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The greatest risk of developing invasive breast cancer have not been identified. Treatment paradigms have not been modified to adapt to the increased detection of relatively benign disease. As a result, many women with DCIS receive XRT with no clinical benefit (are overtreated). Paradoxically, for some women the omission of radiotherapy (following breast conserving surgery) is associated with a higher risk of local recurrence, including invasive breast cancer, that might have been avoided with treatment (undertreatment) because of a misconception that DCIS is so low risk that effective treatments, particularly radiotherapy, may be avoided. This disease presents a clear diagnostic challenge where the impact of diagnostic assays measuring risk of recurrence, and in particular, progression, following a diagnosis of DCIS could dramatically improve the selection of therapies appropriate for individual women. For such markers to be developed, we need to develop a clear understanding of the molecular events that drive recurrence and progression of DCIS. A parallel effort focused on developing robust, portable, and informative assays that measure risk of progression has the potential to drive a personalized medicine solution to the clinical uncertainty facing women and their physicians when presented with a diagnosis of ductal carcinoma in situ.

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