Heterogeneity of ductal carcinoma in situ and its effects on management

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Data derived from histopathological analysis, natural history, radiological characteristics, molecular markers, and clinical outcome indicate that ductal carcinoma in situ (DCIS) is a heterogeneous disease, meaning that no one treatment strategy is best, but rather that treatment should be personalised and entail a systematic and rigorous multidisciplinary approach. Many women with DCIS will develop actual invasive carcinoma over time, whereas others—especially those with low-grade cancers—will not. At the moment, identification of patients at low risk of recurrence risk is very difficult (that is, such people for whom further treatment beyond lumpectomy is not needed). In this context, molecular profiling analysis is a promising method to guide management decisions. In this Review, various treatment strategies for DCIS will be reviewed, highlighting the limitations of randomised trials. Furthermore, discussions about the role of sentinel-node biopsy and tamoxifen in disease management; locoregional recurrence; and special clinical scenarios such as recurrent disease, DCIS after thoracic radiotherapy, ductal carcinoma with concurrent lobular carcinoma in situ, and DCIS in elderly people and in men will be presented.

Introduction
Ductal carcinoma in situ (DCIS) of the breast refers to a proliferation of abnormal epithelial cells within the basement membrane of the mammary ductal system, without the presence of stromal invasion. It is a non-obligate precursor of invasive carcinoma and does not fully express the malignant phenotype of unlimited growth, invasiveness, angiogenesis, and metastatic potential.1

Epidemiology
Widespread use of screening mammography has led to a substantial increase in the frequency of DCIS (figure 1) over the past two decades, and the lesion currently accounts for about a fifth of all screen-detected breast cancers.2 Furthermore, clinical presentation of DCIS has changed from an incidental biopsy finding, a palpable mass, or pathological nipple discharge to mammographic microcalcifications detected through screening.1 In Europe and the USA, the frequency rose by up to 4-5 times from 1980 to 1995. This increase was seen in all age categories, but especially in women aged 50–59 years.3

Diagnostic methods
Full-field digital mammography combined with computer-aided detection is more effective than analogue film mammography in screening premenopausal and perimenopausal women and those with dense breasts,3 but the effect of this strategy on DCIS detection cannot be assessed accurately yet. In a small series, MRI seemed to have good sensitivity to detect DCIS,4 but further studies are needed. This technique could also have an important role in assessment of the extent of disease in the breast. Endoscopic visualisation of DCIS lesions has been facilitated with the advent of mammary ductoscopy, the potential role of which needs further investigation in disease detection and management.4

Figure 1: (A) Low-grade DCIS (magnification x 10). (B) High-grade DCIS with comedo necrosis (magnification x 4).
been used increasingly in recent years, and this technology raises the yield of DCIS diagnosis by upgrading atypical ductal hyperplasia (as diagnosed by standard core biopsy) to DCIS in about 25% of cases.7 Localised excision of non-palpable lesions entails a wire localisation procedure, and intraoperative radiography of the breast (with magnification views when possible) is mandatory.1

Pathology and biological behaviour
The traditional method of classifying DCIS was based on the architecture and growth pattern of the disease, with lesions classified as comedo, solid, cribriform, and micropapillary. Unfortunately, individual lesions can show architectural heterogeneity that restricts the usefulness of this strategy. Systems of classification based on nuclear grade and necrosis show good reproducibility between pathologists, and thus have prognostic value.10–13

Natural history
DCIS corresponds to a heterogeneous group of lesions with variable malignant potential. Although it is clearly preinvasive, not all lesions will progress to invasive malignant disease. The natural history of small, low-grade DCIS in women treated by biopsy alone was initially studied by Page and colleagues and their work was subsequently updated by Sanders and coworkers.14 These researchers noted that 11 (39%) of 28 patients developed invasive breast cancer over a median follow-up of 31 years. All invasive lesions arose in the same breast and quadrant from which the low-grade DCIS biopsy sample was taken. Of these individuals, five (45%) died from metastatic disease. In other follow-up studies15 of untreated DCIS, progression to invasive malignant disease ranged from 14% to 75% of patients. These data suggest that patients with DCIS who received no treatment beyond a diagnostic biopsy procedure were at greatly increased risk for developing ipsilateral breast cancer and that the enhanced risk was seen in cancers of low, intermediate, and, in particular, high nuclear grades.16 However, the time needed for this process seems to be longest for lesions of low nuclear grade and determined by genetic alterations that accumulate during cancer progression from DCIS to invasive disease.

Pathological factors
In ipsilateral breast cancer, some biological characteristics of the tumour are associated with an aggressive biological behaviour. These include hormone-receptor negativity, high nuclear grade, large tumour size, nodal involvement, high S-phase fraction, abnormal DNA ploidy, P53 overexpression, and ERBB2 overexpression. Many of these biological factors have been investigated in patients with DCIS to gain a better understanding of disease biology and to identify those lesions associated with a high risk of subsequent ipsilateral breast cancer development.

Nuclear grade and comedo necrosis both correspond with risk for local recurrence after breast-conserving surgery for DCIS.16–20 but, as noted above, the architectural pattern of DCIS can vary within the same lesion. Holland and colleagues20 proposed that a combination of nuclear grade and cellular polarisation indicates risk for local recurrence. However, cellular polarisation and mitotic frequency alone do not function well as prognostic factors.20,21

As with invasive carcinoma, DCIS can be negative or positive for hormone and ERBB2 receptors, and the implications of this fact have been studied. A significant relation has been recorded between high-grade DCIS and negativity of the oestrogen and progesterone receptors and positivity of the ERBB2 and P53 receptors. Oestrogen-receptor-negative lesions are usually negative for the progesterone receptor, and high-grade DCIS with microinvasion is typically ERBB2-positive and hormone-receptor-negative.22 Provenzano and colleagues22 investigated expression of ERBB2 and hormone receptors in a nested case–control study and recorded that ERBB2-receptor positivity and oestrogen or progesterone receptor negativity were individually associated with risk of recurrence.

These results seem to suggest that tumours that overexpress ERBB2 are an aggressive biological subtype of DCIS, corresponding to high grade and P53 expression. Furthermore, inverse correlations with hormone-receptor expression might indicate the presence of a less aggressive hormone receptor-positive subgroup. This suggestion accords with correlations reported between hormone-receptor positivity and low tumour grade of DCIS. Despite these observations, evidence is scarce to suggest that oestrogen and progesterone receptors, ERBB2 status, or both provide prognostic information about local control but predict response to endocrine treatment.

Genome-wide analyses of DNA, RNA, and proteins of tumours have been facilitated by the advent of new high-throughput technologies. Although these techniques are still in their infancy, they have the potential to supplement previously known, distinct, clinicopathological factors with many thousands of features and enhance our understanding of DCIS biology and treatment.24,25 Findings of chromosome-wide comparative genomic hybridisation have shown DCIS to be a genetically advanced lesion, which has patterns of DNA copy number alterations common to adjacent invasive lesions. These data also suggest the existence of independent pathways of genetic evolution within the disease.24 These observations provide further evidence that DCIS is a direct precursor of invasive breast carcinoma. Array-based genomic hybridisation combined with microdissection could aid accurate genomic analysis of DCIS and deserves further evaluation.
Gene-expression profiling of human breast tumours with complementary DNA microarrays of thousands of human genes provides a distinctive molecular portrait of every tumour and is likely to enhance our understanding of DCIS behaviour and its relation to invasive breast cancer.\(^25\) Protein-expression profiling with either matrix-assisted laser desorption ionisation or surface-enhanced laser desorption ionisation are other promising techniques for molecular characterisation of breast tumours. Wulfkuhle and colleagues\(^26\) undertook proteomics analysis of DCIS and healthy breast tissue and recorded differential expression patterns distinct from findings of previous nucleic acid-based studies and identified new facets of the earliest stage of breast-cancer progression.

**Table 1: Results of DCIS treatment by conservative surgery alone by number of patients**

<table>
<thead>
<tr>
<th>Patients</th>
<th>Median follow-up (months)</th>
<th>Non-palpable (%)</th>
<th>Local recurrence (%)</th>
<th>Invasive local recurrence (%)</th>
<th>Ref</th>
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<tbody>
<tr>
<td>445</td>
<td>57</td>
<td>NA</td>
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<tr>
<td>121</td>
<td>63</td>
<td>83</td>
<td>25.6</td>
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<td>35</td>
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<td>105</td>
<td>91</td>
<td>79</td>
<td>19</td>
<td>55</td>
<td>36</td>
</tr>
<tr>
<td>207</td>
<td>92</td>
<td>NA</td>
<td>18.4</td>
<td>45</td>
<td>37</td>
</tr>
<tr>
<td>265</td>
<td>95</td>
<td>61</td>
<td>26.4</td>
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<tr>
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<tr>
<td>169</td>
<td>80</td>
<td>88</td>
<td>14.8</td>
<td>36</td>
<td>41</td>
</tr>
</tbody>
</table>

Data are from series with more than 100 cases. NA=not assessed.

**Mastectomy**

Mastectomy remains the treatment that provides the best control rates for women with DCIS (about 98% at 7 years). In a meta-analysis by Boyages,\(^9\,\(^11\) 1-5% of patients had recurrent disease, and 76% of recurrences were invasive. Mastectomy can be indicated for multicentric DCIS, large lesions (pathologically larger than 4 or 5 cm depending on breast size), and, in particular, inadequate margins after breast-conserving surgery.

Findings of several studies\(^9\,\(^10\) have shown that about a third of patients with DCIS undergo mastectomy. In two US studies\(^9\,\(^11\) using data from the Surveillance, Epidemiology, and End Results cancer registry 1973–99, the proportion of patients with DCIS who had a mastectomy fell from 71% in 1973 to 43% in 1992 and then to 28% in 1999. In a 2003–04 French survey of 1289 women with pure DCIS, 31% of patients underwent mastectomy.\(^3\) In women needing or requesting mastectomy for DCIS, immediate breast reconstruction with an implant or myocutaneous flap is facilitated by a skin-sparing mastectomy approach, thus resulting in good cosmesis.\(^11\)

**Breast-conserving surgery alone**

With the increasing occurrence of very small mammographically detected lesions, complete local excision has seemed adequate for several researchers. However, table 1 shows that the local recurrence rate after breast-conserving surgery alone ranged from 14.8% to 32.1%, around half of which was invasive.\(^24\) Even in series\(^30\,\(^38\) including only detected DCIS detected mammographically with complete excision, local recurrence at 10 years was between 19% and 28%, about 35% of which were invasive.

Wong and co-workers\(^4\) did a single-group prospective trial from 1994 to 2002, including only DCIS and mainly of grade 1 or 2 with lesions that measured 2.5 cm or less on mammography and final surgical margins of at least 1 cm treated by breast-conserving surgery alone. The accrual goal was 200 patients, but in July, 2002, the study was closed. Indeed, after 40 months’ median follow-up, 13 patients had developed local recurrence (nine DCIS and four invasive), corresponding to 13% of patients at 5 years, and thus reaching the stopping rules of the trial. This study included lesions with no sufficiently low-risk factors (grade or size and age).

By contrast, a Californian team\(^44\,\(^45\) used the Van Nuys prognostic index, which combines tumour size, surgical margin width, nuclear grade, and presence or absence of necrosis to define low-risk DCIS. In 176 patients with 65 months’ follow-up they recorded only three local recurrences. However, in the national surgical adjuvant breast and bowel project (NSABP) trial B-17,\(^6\) this index was not a predictive factor for possible omission of radiotherapy in some subgroups.

**Breast-conserving surgery plus radiotherapy**

This combined treatment strategy has been used widely for patients with DCIS. Local recurrence ranges from 3% to 19%, with an average of 10% at 7 years.\(^4\) Invasive local recurrence is about 60%. In three series,\(^3\)\(^8\) including only small mammographically detected lesions with complete excision, 3% of patients had local recurrence at 64 months’ follow-up, 6% at 90 months’ follow-up, and 10% at 120 months’ follow-up.
Randomised trials

In four randomised trials, researchers compared breast-conserving surgery alone with surgery plus radiotherapy.47–52 Three had previously been widely published.47–50 The European Organization for Research and Treatment of Cancer (EORTC) trial has been updated49 and Swedish data are now available.51 All studies compared excision with recommended negative margins versus the same surgery and addition of whole-breast radiotherapy at 50 Gy in 25 fractions without a boost. The UK DCIS trial50 was designed with a 2×2 factorial plan to assess at the same time the effect of tamoxifen. Figure 2 summarises the results of these studies. In the updated EORTC trial,49 radiotherapy was beneficial for all subgroups but to varying degrees (figure 3).

Findings of these four studies strongly confirm that radiotherapy substantially reduces local recurrence risk after breast-conserving surgery. In the NSABP B-17 and EORTC trials, this benefit was noted in all subgroups of patients, but to different extents. However, these studies have important limitations relating mainly to the pathological techniques used. None of the randomised trials—particularly NSABP B-17—had effective mammographic-pathological correlations, routine specimen radiography, postoperative imaging (which is a necessity), and adequate definition, let alone measurements of tumour size or margins. In NSABP trial B-17, when central slide review was undertaken (in 73% of cases), 7% and 2% of lesions were reclassified as atypical epithelial or microinvasive disease. Figure 3 summarises the results of these studies. In the updated EORTC trial,49 radiotherapy was beneficial for all subgroups but to varying degrees (figure 3).

Pathological protocols

Both in randomised trials and in retrospective work, several different protocols are available to assess DCIS size, topography, residual disease in re-excision samples, final margins, and correlations with mammographic features. In many studies, standard procedures were not undertaken.44 Orientation of the breast allows directed intraoperative re-excisions for close margins on examination of the breast with radiography or macroscopically, and selective inking of margins is a standard recommendation of the consensus conference on DCIS.15,27 Unfortunately, neither of these practices could be evaluated in most studies.44 In a French survey, of patients treated by conservative surgery (with or without radiotherapy), orientation and inking of the breast was done in 81% and 75% of cases, respectively.52 Moreover, use of core-needle biopsy in

The UK DCIS trial44 was analysed with complex statistical methodology, did not have clear analysis of subgroups according to main histopathological features, and its method of randomisation was unconventional (chosen by the doctor or patient). Moreover, 53 cases (3%) of microinvasive lesions (<1 mm) were also included. In the Swedish study,51 random central pathological review of 198 (19%) of 1046 cases recorded 16% of non-DCIS lesions—benign (7%), atypical ductal hyperplasia (5%), and invasive or microinvasive cancers (4%). Finally, none of these trials was sufficiently powered to detect differences in overall survival. Such an issue could be addressed by a meta-analysis.

Most limitations encountered in these investigations have been addressed by ongoing studies, namely the Eastern Cooperative Oncology Group trial E5194 and the Radiation Therapy Oncology Group trial 98-04. Results of this work will be available in a few years time.
preoperative diagnosis was hardly mentioned in early studies, whereas this practice contributes to reducing the number of operations and enhancing excision quality. In previous work, no data are provided for complete sequential tissue processing techniques (eg, number of blocks or cassettes). All these variables are important for standardisation of DCIS assessment and partly account for discrepancies in estimates of local recurrence in some series.

Role of tamoxifen
In NSABP trial B-24, 1804 women treated by lumpectomy and radiotherapy were randomly allocated either placebo or tamoxifen (10 mg twice daily) for 5 years. After median follow-up of 7 years, local recurrence was 11% in the placebo group and 8% in the tamoxifen group (p=0.02). The absolute reduction was significant for invasive but not for in-situ local recurrence. Contralateral breast cancer was reduced from 5% in the placebo group to 3% in the tamoxifen group; however, an increase in prevalence of endometrial cancers (0·8% vs 0·3%) and thromboembolic accidents (2% vs 1%) was recorded in patients taking tamoxifen. Moreover, no benefit was noted in women older than 50 years (6% vs 8%), in completely excised lesions (7% vs 9%), and in those without necrosis on final histological analysis (6% vs 8%). Furthermore, the overall death rate was identical in both groups (5%). 16% of women had involved excision margins, and 11% did not have their margins assessed. Subsequent analysis of data from the NSABP B-24 trial for 676 women (36%) in whom retrospective analysis of oestrogen-receptor status was possible showed that 77% of patients were oestrogen-receptor-positive and that the benefit of tamoxifen was present in this subgroup only.

Conversely, results of a trial from the UK, Australia, and New Zealand showed that, of 1053 patients with DCIS not receiving radiotherapy, adjuvant tamoxifen did not greatly reduce the frequency of ipsilateral invasive breast cancer events (5% vs 4%, p=0.3) or of DCIS (6% vs 9%, p=0.1). However, the total number of DCIS events (ipsilateral and contralateral) was significantly reduced by tamoxifen (6% vs 10%, p=0.03). In the 523 patients receiving radiotherapy, no difference was recorded between the two groups.

These discrepancies might be accounted for by the difference in age distributions and hormone-receptor status between the two trials. Tamoxifen was shown in both studies to be more effective at reducing the incidence of ipsilateral breast recurrence in women aged 50 years or younger. Only 10% of patients in the UK, Australia, and New Zealand trial were younger than 50 years compared with 34% in NSABP B-24. Investigators on the UK, Australia, and New Zealand study have not provided any data for tamoxifen effects in relation to hormone-receptor status. Tamoxifen can, therefore, be considered in selected cases—eg, young women with positive oestrogen or progesterone receptors and without risk factors for the potential side-effects of tamoxifen, namely endometrial cancer and thromboembolic accidents. However, both these trials were underpowered to show such a survival benefit. Moreover, researchers on two ongoing investigations (International Breast Cancer Intervention Study [IBIS] II and NSABP B-35) are assessing the possible contribution of anastrozole versus tamoxifen after breast-conserving surgery with and without radiotherapy.

Management of axilla
Theoretically, pure DCIS is a localised disease confined within the basal membrane, without any risk of invasion of lymph nodes or vessels. As a result, axillary dissection is not indicated. This situation is true for small lesions, but extensive DCIS can contain small foci of invasive disease, accounting for the finding of positive axillary nodes in 1–2% of patients in some early series. However, the number of patients who receive axillary dissection for DCIS has been declining worldwide. Of 25 200 US patients treated from 1992 to 1999, this rate fell greatly from 34% in 1992 to 15% in 1999 (p<0.001) and more specifically in women treated with mastectomy (from 52% to 10%).

To avoid further surgery when detecting an invasive component after excision of large DCIS lesions, the sentinel-node-biopsy technique can be used. Reported positivity rates with this procedure vary from 1·8% to 12% depending on selection criteria and analytical methods used—eg, cytokeratin immunohistochemical staining. However, the importance of positive isolated cells in the sentinel node remains unknown in both invasive and non-invasive breast cancer. Sentinel-node biopsy should not be done routinely in patients undergoing breast-conserving surgery for pure DCIS, but it can be considered in women with a high risk of invasion on final histological analysis, such as large high-grade lesions usually needing mastectomy.

Locoregional recurrence
After mastectomy, local recurrences are almost always invasive; after conservative surgery (with or without radiotherapy), about 50% of such recurrences are invasive and 75–80% of them arise at the site of the original lesion or in its vicinity in the index quadrant. Invasive local recurrence is potentially life-threatening and is associated with 15–20% of concomitant axillary involvement and subsequent metastasis (13–18%).

Treatment
In a French series, salvage mastectomy was undertaken in 64% of women (53% in those who had breast-conserving surgery and 75% in those treated with surgery and radiotherapy). In the NSABP B-17 trial, salvage mastectomy was done in 29 (62%) of 47 patients.
treated by previous breast-conserving surgery and radiotherapy and 50 (48%) of 104 who underwent surgery alone. In a report by Solin’s group, mastectomy was undertaken in 76 (84%) of 90 operable cases of local recurrence.

**Prognosis**

Prognosis of in-situ and invasive local recurrence is very different. In a French series, only three (4%) of 82 women with in-situ local recurrence developed metastasis versus 19 (17%) of 113 with invasive recurrence. Similarly, Silverstein did not find any subsequent metastases in 62 women who developed in-situ local recurrence, whereas seven (15%) of 47 with invasive recurrence presented with further dissemination. Finally, in Solin’s series, seven (8%) of 47 with invasive recurrence presented with further metastases in 62 women who developed invasive recurrence.

The overall rate of metastasis in patients with DCIS remains very low, but it greatly increases after invasive local recurrence. In three large series, the proportions of patients with local recurrence who developed metastatic disease were 13% of 53; 14% of 118, and 18% of 33 cases.

In a large population-based analysis, Warren and colleagues recorded local recurrence of 15% in 626 women treated by breast-conserving surgery and of 11% in 477 receiving surgery and radiotherapy (mean follow-up 91 months). Risk of invasive local recurrence was 49% versus 31% in this series, and risk of breast-cancer-specific mortality was 3% versus 1% (p=0.02), despite the fact that patients treated with breast-conserving surgery and radiotherapy tended to have tumours of worse grade and larger size than those receiving surgery alone.

**Risk factors for local recurrence**

**Patient-related factors**

Young age (generally ≤40 years) is an independent risk factor for local recurrence after breast-conserving surgery with or without radiotherapy for DCIS. A 30% average rate of recurrence was reported in several studies in this population, even with addition of radiotherapy. However, in cases of mammographically detected DCIS, a 10-year local recurrence of 18% in women younger than 40 years was noted in a large multicentre series.

With respect to clinical presentation, in the San Francisco Bay study, including 1036 women treated by lumpectomy alone, 5-year local recurrence was 21% in lesions detected by palpation and 17% in those detected with mammography. Risk for local recurrence in the EORTC trial was higher (relative risk 1.8) for DCIS detected by clinical symptoms compared with screening mammography (27% and 16% in the local excision group vs 17% and 11% in those treated with local excision and radiotherapy).

### Table 2: Local recurrence according to margin width in 445 patients treated by breast-conserving surgery alone

<table>
<thead>
<tr>
<th>Margin width (mm)</th>
<th>Patients</th>
<th>Local recurrence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 mm</td>
<td>85†</td>
<td>39</td>
</tr>
<tr>
<td>1-2 mm</td>
<td>102</td>
<td>26</td>
</tr>
<tr>
<td>3-9 mm</td>
<td>61</td>
<td>16</td>
</tr>
<tr>
<td>≥10 mm</td>
<td>197</td>
<td>4.6</td>
</tr>
<tr>
<td>Total</td>
<td>445</td>
<td>17</td>
</tr>
</tbody>
</table>

*p<0.001. †Including 32 patients with transected margins.

**Tumour-related factors**

Margin width remains one of the most important risk factors for local recurrence after breast-conserving surgery with or without radiotherapy. In an analysis of 583 patients (346 treated by surgery only and 237 by surgery and radiotherapy), Silverstein showed that margin width (divided into three categories: <1 mm, 1–9 mm, and ≥10 mm) was the most important risk factor in both treatment groups. Of 445 women treated by breast-conserving surgery alone (with 57-month median follow-up), MacDonald and Silverstein recorded local recurrence in 17% of patients, with substantial differences according to margin width (table 2). However, measurement of margin width is sometimes very difficult and, in most series, use of re-excision complicated data interpretation. At a conference in Philadelphia, PA, USA, no consensus between pathologists was reached about the definition of the best free margin (eg, 2, 5, or 10 mm). French national guidelines published in November, 2004, recommended a minimum free margin of 3 mm; in cases of a 1–3 mm margin, the need for re-excision should be discussed by a multidisciplinary team (according to tumour size, age, and nuclear grade), and with a margin of less than 1 mm, re-excision should be done. Other researchers recommend a minimum margin width of 2 mm.

A standard analysis report for margin status will be helpful to interpret data from different institutions.

Tumour size is generally regarded as an important indicator of local recurrence in patients treated by breast-conserving surgery with or without radiotherapy, but actual DCIS size is sometimes very difficult to assess and is rarely expressed in mm. In an EORTC study, only 25% of reviewed cases had the maximum tumour diameter specified in mm. In NSABP trial B-17, size could not be assessed in most patients. In a Danish investigation of 142 women with DCIS treated by breast-conserving surgery alone, local recurrence at 10 years was 11% for lesions smaller than 10 mm and 48% for those larger than 10 mm.

With respect to nuclear grade, in the large San Francisco Bay Area series, risk of local recurrence at 5 years was 9% in tumours of low nuclear grade, 16% in those with an intermediate grade, and 25% in those with a high nuclear grade. In MacDonald and
Silverstein’s updated series,61 local recurrence was recorded in 8% of tumours of nuclear grade I–II and in 32% for those of grade III (p=0.001).

**Treatment-related factors**

Excision quality remains an important factor for improvement of local control after breast-conserving surgery for DCIS, with strong correlation with margin width. In one series,79 total excision volume correlated with 5-year local recurrence: 9% for volumes less than 60 cm³ and 0% for those of 60 cm³ or greater. Similarly, in a study by Vicini and colleagues,71 small excision (<60 cm³) led to a 2.69 relative risk of local recurrence in women younger than 45 years versus larger excision.

Histological examination of re-excision samples in patients undergoing breast-conserving surgery for DCIS showed residual disease in 40–82% of women in whom DCIS reached the initial resection margin,72 especially in low-grade lesions.71 All such data emphasise the importance of a rigorous initial surgical approach aiming for one excision with a minimum margin of 2 mm.

For DCIS and infiltrating carcinomas, the standard dose of whole-breast radiotherapy is 50 Gy in 25 fractions for 5 days a week.88,89 In infiltrating breast carcinomas, results of a large trial78 indicated the benefit of a 16 Gy boost on local control, especially in women younger than 50 years. However, no such specific data exist for DCIS. A radiation boost was not allowed in NSABP B-17 results of a large trial74 indicated the benefit of a 16 Gy median dose boost of 10 Gy. However, precise analysis remains very difficult, because boost indications varied widely and were sometimes applied in cases of so-called limited excision, occasionally with doubtful or involved margins.

**Special clinical scenarios**

**Elderly people**

Published work is very scarce in people aged 70 years or older. In an analysis by the International Collaborative Group,61 of 1003 patients with screen-detected DCIS treated by breast-conserving surgery and radiotherapy, 98 (10%) were age 70 years or older. 10-year local recurrence was 5% in 321 women older than 60 years, with no specific data for those older than 70 years. In the French cancer centres study,61 of 1223 patients treated from 1985 to 1996 by breast-conserving surgery (n=263), surgery and radiotherapy (600), or mastectomy (358), 76 (6%) were 70 years or older. With 75-month follow-up, local recurrence in these women was recorded in one of 26 (4%) with mastectomy and in four of 18 (22%) with breast-conserving surgery; no recurrence was seen in 32 patients treated by breast-conserving surgery and radiotherapy.88,89 In a French DCIS survey,19 173 (13%) of 1289 women were older than 70 years, of whom 18 (10%) underwent breast-conserving surgery, 112 (65%) had surgery and radiotherapy, and 43 (25%) had mastectomy.

**Men**

To date, about 300 cases of pure DCIS have been reported in men.80 The proportion of this disease in male breast cancer series varies from 0% to 17%, with an average of 7%. The two largest series are of 31 patients seen in French cancer centres from 1970 to 1992 and of 84 men recorded by US Armed Forces Institutes of Pathology.87,88 Simple mastectomy provides almost 100% local control, whereas lumpectomy alone leads to a high rate of local recurrence.89

**DCIS after thoracic radiotherapy**

Breast cancer is the most frequent secondary solid neoplasia in women previously treated for Hodgkin’s disease by radiotherapy alone or in combination with various chemotherapy regimens. Risk for secondary breast cancer is widely increased at adolescence or young adulthood. The median interval of breast cancer onset after Hodgkin’s disease was 16 years in the French cancer centres study.89 Of 133 assessable cases, 15 (11%) were pure DCIS, 11 of which arose in women treated exclusively by radiotherapy with a 20-year median delay. In two other series, DCIS rates of 13% and 18% were noted.89 Most patients were treated by mastectomy, but breast-conserving surgery with radiotherapy was possible in 29% of women in the French series88 with no specific side-effects.

**DCIS associated with lobular carcinoma in situ**

Specific data for this topic are scarce. In a Danish series87 including 142 women with DCIS, 100 with lobular carcinoma in situ, and 26 mixed forms, local recurrence at 10 years was 35% for patients with DCIS, 18% for those with lobular carcinoma in situ, and 35% in those with mixed histology. Thus, the rate of recurrence was identical, but the proportion of invasive local recurrence was higher in the mixed group than in the pure DCIS group (67% vs 43%). In the French cancer centres series,76 local recurrence at 7 years was similar in women treated with breast-conserving surgery alone with and without associated lobular carcinoma in situ (24% vs 27%), but it rose in those who underwent surgery and radiotherapy (24% vs 12%).

**Conclusions**

The best treatment for DCIS, which is a precursor of invasive breast cancer, needs a systematic and rigorous multidisciplinary approach. Even without clear consensus, complete excision of DCIS with a minimum margin width of 2 mm seems essential to achieve acceptable local relapse rates, especially in young women.87 Findings of randomised trials and retrospective studies have confirmed that whole-breast radiotherapy after breast-conserving surgery reduces 10-year local...
recurrence (both invasive and in situ) from about 25–30% to 10–14%. The radiotherapy benefit is seen in all subgroups; however, its extent varies and is reduced in cases of small, low-grade DCIS with more than 1 cm of clear margins. However, for now and the near future, no defined subgroup of patients with DCIS after excision is known who can obviously avoid adjuvant radiotherapy.22

Total mastectomy with or without immediate reconstruction remains the treatment of choice for multicentric, extensive (greater than 4 or 5 cm depending on relative breast size), and recurrent disease (after previous breast-conserving surgery and radiotherapy). Axillary node dissection is not indicated; however, sentinel-node biopsy should be considered in patients undergoing mastectomy with high-risk lesions. In women having breast-conserving surgery for DCIS, addition of adjuvant tamoxifen does not improve survival, although its use can be considered in young patients with hormone-sensitive disease and without risk factors for its serious side-effects, namely thromboembolic accidents and endometrial cancer. Advances in molecular profiling are likely to enhance our understanding of the biological behaviour of DCIS and guide its treatment.

Conflicts of interest
We declare no conflicts of interest.

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References


