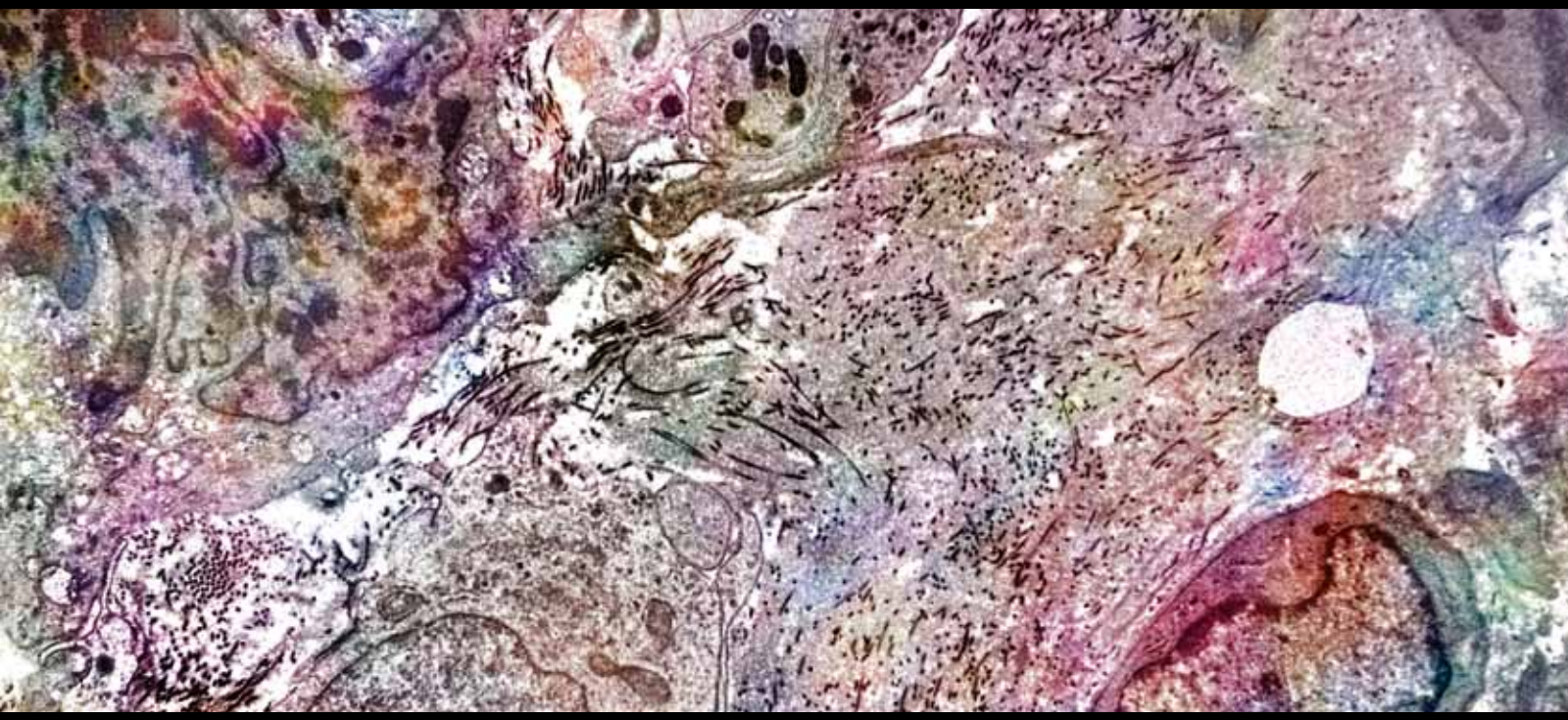
International Journal of Surgical Oncology

Breast Ductal Carcinoma In Situ

Guest Editors: Virgilio Sacchini, Lucio Fortunato, Hiram S. Cody III, Kimberly J. Van Zee, Bruno Cutuli, and Bernardo Bonanni



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Editorial Board

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Editorial

Breast Ductal Carcinoma In Situ

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Ductal carcinoma in situ (DCIS) of the breast is becoming one of the most important diseases diagnosed in preventive medicine screening. The current age-adjusted incidence rate of DCIS is 32.5 per 100,000 women. For women 50–64 years of age, the incidence is approximately 88 per 100,000. Currently, for every 4 diagnoses of invasive breast cancer, there is 1 diagnosis of DCIS. Risk of DCIS is rare in women younger than 30 years of age and is low in women under 40 years of age, but increases steadily from ages 40–50. The risk of DCIS increases much more slowly after the age of 50, and it plateaus after the age of 60.

Assuming constant incidence and survival rates, it is estimated that more than 1 million women will be living with diagnosed DCIS by 2020, with obvious social and political health ramifications. The question scientists are facing now, and the question women are beginning to ask their breast surgeons, is whether we are overdiagnosing and overtreating this disease.

Should we be less aggressive and more tolerant toward this disease? We are aware that DCIS is a spectrum of different diseases and that we may have overdiagnosed and overtreated to a point, but we have also likely undertreated others. Despite randomized clinical trials and evidence-based recommendations, there are important regional and geographic differences in clinical management, reflecting both a cultural bias regarding, and the heterogeneity of, this disease.

In this current issue, the authors present a detailed overview of the state of the art of the diagnosis and treatment of this disease as well as an overview of future tendencies and research.

M. Badruddoja extensively reviews the most recent knowledge of epidemiology and risk factors for DCIS.

L. Fortunato et al. and M. Amichetti et al. review all the randomized clinical trials on DCIS, giving an unbiased interpretation of the data that is helpful in the daily management of DCIS patients.

K. Lambert et al., in their literature review facilitated by the Medline, PubMed, Embase, and Cochrane databases, consider randomized, nonrandomized, prospective, and retrospective studies with the goal of increasing understanding of the most important predictive factors for local recurrence, and of better selection of the use of radiation therapy and tamoxifen.

The still debatable issue of sentinel node biopsy in DCIS is addressed by D. Boler et al., who present their experiences and discuss literature evidence.

G. Scripcaru and I. M. Zardawi investigate the occurrence of each architectural growth pattern in mammary DCIS. Correlating the architecture with nuclear grade, they postulate that the comedo pattern can ultimately occur in all types of DCIS and therefore should not be regarded as a separate DCIS type.

D. Coradini et al., in an elegant experiment, investigate the expression patterns of a selected panel of genes associated with cell polarity and the apical junction complex. They are able to confirm that atypical ductal hyperplasia and DCIS are part of a tumorigenic, multistep process with possible chemoprevention implications.

E. Bastiaannet et al., analyzing 8421 patients with DCIS, found no excess mortality irrespective of treatment in women older than 50 years of age, with the important clinical

implication that local relapse in these women may not impact prognosis.

K. Van Zee and D. Choi et al. from Memorial Sloan-Kettering Cancer Center investigate many aspects of the biology, diagnosis, and treatment of DCIS over a 20-year period with the final development of a nomogram that incorporates many factors simultaneously to estimate the risk of local relapse in DCIS treated with conservation therapy.

Several recent patterns-of-care studies have identified substantial variation in surgeon decision making regarding the optimal management of DCIS [1–5]. In September 2009, the National Institutes of Health convened a conference to discuss the diagnosis and management of patients with DCIS because of the complexity and discrepancy in its management [6].

The papers presented here represent important contributions toward a better understanding of this disease and its treatment, and emphasize the need for a multidisciplinary approach to DCIS.

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Review Article

Ductal Carcinoma In Situ of the Breast: A Surgical Perspective

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Ductal carcinoma in situ (DCIS) of the breast is a heterogeneous neoplasm with invasive potential. Risk factors include age, family history, hormone replacement therapy, genetic mutation, and patient lifestyle. The incidence of DCIS has increased due to more widespread use of screening and diagnostic mammography; almost 80% of cases are diagnosed with imaging with final diagnosis established by biopsy and histological examination. There are various classification systems used for DCIS, the most recent of which is based on the presence of intraepithelial neoplasia of the ductal epithelium (DIN). A number of molecular assays are now available that can identify high-risk patients as well as help establish the prognosis of patients with diagnosed DCIS. Current surgical treatment options include total mastectomy, simple lumpectomy in very low-risk patients, and lumpectomy with radiation. Adjuvant therapy is tailored based on the molecular profile of the neoplasm and can include aromatase inhibitors, anti-estrogen, anti-progesterone (or a combination of antiestrogen and antiprogesterone), and HER2 neu suppression therapy. Chemopreventive therapies are under investigation for DCIS, as are various molecular-targeted drugs. It is anticipated that new biologic agents, when combined with hormonal agents such as SERMs and aromatase inhibitors, may one day prevent all forms of breast cancer.

1. Introduction

Ductal carcinoma in situ (DCIS) of the breast is a noninvasive carcinoma with a wide spectrum of disease, ranging from low-grade to high-grade malignancy with foci of invasive malignancy. Histologically, DCIS is characterized by a proliferation of malignant cells in the ductal epithelium that are confined to the basement membrane and are not invading the normal breast parenchyma.

2. Epidemiology

Prior to advent of mammography, the diagnosis of DCIS was established only after excision of palpable lumps and histological examination of the tissue. Egan et al. [1], a radiologist based at the MD Anderson Cancer Center in Houston, Texas, is credited as the inventor of mammography in the late 1960s. By 1975, the widespread use of this imaging technique not only resulted in early detection of lesions in the breast but also led to a 60–70% reduction in morbidity and mortality from malignant diseases of breast [2]. The adoption of screening and diagnostic mammography resulted in an increase in the incidence of DCIS worldwide, with 80% of DCIS diagnosed by mammography. Currently, DCIS accounts for 20–25% of all newly diagnosed cases of breast cancer [3] and 17–34% of mammographically detected breast neoplasms [4, 5]. Approximately 1 of every 1300 screening mammograms results in a diagnosis of DCIS, and over 62,000 new cases of DCIS were diagnosed in 2009 [6].

Between 1983 and 2000 in the United States, there was a 500% increase in DCIS among women ≥50 years of age, though the incidence decreased by 2005 [7, 8]. Among women <50 years of age, DCIS incidence increased 290%

from 1983 to 2003, followed by a continuous decline that was most likely due to a reduction in the use of hormone replacement therapy [9]. Virnig et al. [10] showed that the incidence of DCIS markedly increased from 5.8 per 100,000 women in the 1970s to 32.5 per 100,000 women in 2004, but then plateaued. DCIS is not common in younger women (<30 years of age). The risk of DCIS is 0.6 per 100,000 women 49–60 years of age, and increases to 1.4 per 100,000 women 70–84 years of age.

The risk of death from DCIS is very low; for women who were diagnosed between 1984 and 1989, the 10-year risk was 1.9% based on data from the National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) database [11]. The estimated incidence of DCIS was 32.5 per 100,000 women in 2004, based on NCI SEER data from 1975–2004. This is considerably higher than that reported in 1975 (5.8% per 100,000), but is consistent with the findings of the Swedish Two-County trial [12].The same trend is noted in numerous studies [13, 14]. In summary, there has been an overall increase in the incidence of DCIS in women after the age of 50 around the globe. This increase could be due to a greater awareness among women about breast malignancy, an increase in screening or diagnostic mammograms, the selective use of magnetic resonance imaging (MRI) in high-risk patients, or the use of genetic markers to identify high-risk patients, which will be discussed in detail below.

3. Risk Factors for DCIS

There are multiple risk factors for development of DCIS, including demographic, reproductive, biological, and behavioral risk factors. It is clear that the incidence of DCIS, like invasive carcinoma, is related to age. Incidence increases after the age of 50 years; several studies have shown that the incidence is 2.5 per 100,000 for women 30–40 years of age and steadily increases to a peak of 96.7 per 100,000 women 65–69 years of age. The incidence of DCIS is highest in Caucasian women compared with African American and Asians and Pacific Islanders, with the lowest incidence in Hispanics [15]. Prior to 1973, there were no data on the incidence of DCIS in urban and rural populations; however, one study showed that while the incidence of DCIS was increasing in both populations, the incidence was higher in urban women compared with rural women [16]. Another study showed that DCIS is also more prevalent in women who are less educated, particularly those with no high school degree [17]. One Australian study showed that the incidence of DCIS was 7.3% in those with relatively higher incomes compared to 4.5% in those with lower incomes.

Older age at menopause was associated with a higher incidence of DCIS [19]. One study showed that peri- and postmenopausal women had higher incidences of DCIS compared with premenopausal women [20]. The study, which was based on the Connecticut Tumor Registry, showed that there was a significant relationship between an increased risk of developing DCIS and older age at menopause; women who reached menopause after the age of 50 years had a higher risk of developing DCIS compared to those who reached menopause before the age of 45 years [20]. These findings are consistent with the likely role that hormone status plays in determining DCIS risk. A large prospective study from the United Kingdom reported a 56% increase in the risk of developing DCIS in women taking hormone replacement therapy (HRT), with the risk increasing with the duration of HRT [21]. Compared to those who never received HRT, women who took HRT for less than 5 years had significantly lower risk of DCIS. While the Iowa Women's Health Study found that there was no increased risk of DCIS in women who received HRT compared with those who did not [22], a subsequent metaanalysis found that women who had previously taken HRT had a higher risk of developing DCIS [22]. However, women who had used oral contraceptives (OCs) or were current users were found to have the same risk of DCIS as those who had never used OCs [23]. Nulliparity or women who had a late pregnancy (after 30 years of age) also had a higher incidence of DCIS [24]. Similar results were reported in a Danish cohort study [25]. Recently, the National Research Council of Australia published a summary of the evidence on HRT and the risk of breast cancer [26]. Only estrogen, combined estrogen-progesterone, combined estrogen-testosterone, and Tibolone are used for HRT. In women 50–79 years of age, the absolute risk of breast cancer is 38 per 100,000 for those taking combined estrogen and progestin (average over 5 years) compared with 30 per 100,000 for those who have never used combined HRT. It is not possible to accurately determine the duration of HRT after which breast cancer risk is increased; however, HRT for more than 3 years appears to be associated with an increased risk [27]. The Women's Health Initiative trial also showed that there is significant risk of developing breast cancer in women who had prior exposure to combined HRT for more than 6 years, while there is no overall increase in the incidence of breast cancer in women who were never exposed to HRT [28]. There are only inconsistent reports regarding the risk of breast cancer and the use of estrogen-only HRT. In one study, short-term use of estrogen-only HRT did not increase the risk of breast cancer [29]. In the Nurses Health Study, the risk of breast cancer was increased significantly in women with prior hysterectomy after 20 years or more of HRT, and the relative risk was higher for estrogen receptor (ER)+/progesterone receptor (PR)+ cancers [30]. One prospective study reported that combined use of estrogen and testosterone HRT in postmenopausal women increases the risk of breast cancer by 17% per year [31]. In the LIFT study of older postmenopausal women with low bone mineral density, breast cancer risk was decreased in the group receiving Tibolone compared with placebo; however, the study was terminated early due to an increased incidence of stroke [32]. There does not appear to be a significant difference in the risk of breast cancer based on the route of HRT administration (e.g., transdermal, oral, implant [33]).

A history of benign biopsied breast disease is associated with a higher risk of breast cancer [34]. In addition, the same study indicated that high intake of vitamin A and alcohol increases the risk of breast cancer. Obesity and increases in BMI by 25% are also risk factors for breast cancer. In a study conducted in Alberta, Canada, by Friedenreich and

colleagues, increased physical activity decreased the serum levels of all sex hormones [35], previously sedentary postmenopausal women who adhered to a moderate-to-vigorous intensity exercise program showed decreases in serum levels of estrogen, progesterone, testosterone, and sex hormone binding globulin and had a lower risk of postmenopausal breast cancer. In addition, the exercise program led to weight loss which also contributed to the decrease in breast cancer risk.

Mammographic detection of increased density of breast tissue is also a risk factor for breast cancer. In a recent study by Boyd and colleagues, women with 75% or higher density on a mammogram had an increased risk of breast cancer compared with women with mammograms with less than 10% density [36]. Women with extensive mammographic density detected between screening tests are also at high risk of developing DCIS, and considerable number of DCIS cases are associated with this single risk factor. Thus, high-risk patients who have dense breast tissue detected by mammogram should have a follow-up MRI of the breast so that lesions are not missed.

Observational studies have suggested that beta carotene, vegetables, fruits, and antioxidants may have protective effects against breast cancer. However, a recent randomized controlled trial found no such protective effects of a diet supplemented with beta carotene, vitamin C and E, fruits, and other antioxidants [37]. This trial followed 624 women for a period of 9.4 years and found that compared to placebo group, the relative risks of developing breast cancer were 1.11% in vitamin C group, 0.79% in vitamin E group, and 1% in beta carotene group. The Iowa Study showed that aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) have a protective effect against breast cancer [38]. An animal and in vitro study also showed that aspirin not only prevents breast cancer, but also prevents metastasis in breast cancer [39].This was a prospective observational study in which 4164 female patients with stage I, II, or III breast carcinoma were followed for 26 years [39]. The relative adjusted risk of metastasis in those who took aspirin for 1 day, 2 to 5 days, and 6 to 7 days per week compared with those who did not take aspirin were 1.07 (95% CI, 0.70 to 1.63), 0.29 (95% CI, 0.16 to 0.52), and 0.36 (95% CI, 0.24 to 0.54), respectively. The most recent study, based on a systematic comparison of evidence from observational studies, indicated that daily aspirin intake not only prevents colorectal cancer, but also prevents breast, esophageal, biliary, and gastric cancer [40]. The study also showed that aspirin prevents and delays metastasis from breast, esophageal, gastric, and hepatobiliary cancer.

4. Diagnosis

Diagnosis of DCIS is primarily based on imaging results in developed countries of the world, while developing and or underdeveloped countries of the world continue to rely on excision and histologic analysis of the tissue biopsy. This disparity is due to the lack of screening facilities and imaging equipment, lack of funding, and cultural barriers in certain developing and underdeveloped countries [41]. In these countries, only 20% of ductal carcinomas are diagnosed on clinical examination and 80% of patients present to the clinician with a palpable lump, nipple discharge, or skin change over the breast [42]. Very recently, the US Cancer Prevention Task Force made a very cautionary remark regarding the overuse of imaging studies (i.e., mammography) for evaluation of diseases of breast [43]; however, even with such cautionary remarks, mammography remains the gold standard for diagnosis of breast diseases. Clinicians continue to advocate for yearly screening mammography in low-risk or non-risk patients after the age of 50 years and in high-risk patients before age of 40 years. Nevertheless, there is concern about radiation exposure during screening mammography. Advances in digital mammography have led to a 22% reduction in radiation exposure compared with film mammography [44]. While digital mammography is more expensive than film mammography, some claim that digital mammography is able to detect more lesions. In one study [45], the detection rate of each modality is same, but the sensitivity and specificity of digital versus film mammography vary with age, tumor characteristics, breast density, and menopausal status. The detection rate was higher with digital mammography than film mammography in women between the ages of 60 and 69 years (89.5% versus. 83%; $P = 0.014$) and in those with ER+ cancers. Clinicians and radiologists will have to decide which imaging study is appropriate for an individual patient.

MRI is used frequently after the detection of lesions by digital or screening mammography, primarily because MRI can help guide surgical decision making among the possible options—breast conserving surgery, mastectomy, or bilateral mastectomy. Surgical decision making is based on the multicentricity of the disease, tumor size, status of the contralateral breast, and family history. The accuracy of MRI over mammography in evaluating the first 3 factors defines its clinical value. In addition, MRI has a higher diagnostic accuracy for DCIS compared with either film or digital mammography. Riedl and colleagues [46] studied 672 imaging rounds in a high-risk population and found that the detection rate of DCIS by mammography, ultrasound (US), and MRI were 50%, 42.9%, and 85.7%, respectively. This detection rate is similarly high for both in invasive cancer and preinvasive cancer (DCIS). Based on their findings, the authors recommended that MRI should be included in the imaging of high-risk patients. Kuhl and colleagues [47] performed a retrospective study and found that the detection rate of DCIS is 92% by MRI and 56% by mammography, and that 48% of high-grade DCIS are missed on mammography but detected by MRI.

Collectively, the literature reports that MRI is able to detect multicentric lesions, estimate the size of the tumor, and predict the invasive nature of the lesion. Hwang and colleagues [48] found that MRI has 94% sensitivity in detecting multicentric lesions compared to mammography, which has 38% sensitivity. In a similar study, Menell and colleagues [49] found that the sensitivity of MRI and mammography for detecting multicentric lesions in DCIS are 94% and 38%, respectively. However, in another study of 86 women, Santamaría and colleagues [50] did not find

any difference in sensitivity between MRI and mammography for detecting multicentric lesions in DCIS, but did report a higher performance of MRI than mammography. Hollingsworth and Stough [51] reported that the incidence of occult multicentric disease in DCIS was 6.3% and could be detected by MRI. Multicentricity is defined as a lesion 5.0 cm from the index lesion or discontinuous growth into another quadrant of the breast [52]. Assessment of the growth patterns of DCIS during tissue processing and histologically based tumor measurements are difficult, as the three-dimensional (3-D) extent of the disease must be reconstructed using 2-D pathology slides. For this reason, MRI measurements of tumor size may be more accurate than pathologic measurements. Uematsu and colleagues [53] found that MRI measurement of DCIS is more accurate than mammographic measurement of the extent of disease, and Lehman and colleagues [54] reported that the sensitivity rate of MRI in detecting contralateral DCIS is 77%. Interestingly, MRI results led to biopsy of the contralateral breast in 18 patients, of which only 28% were positive.

Ultrasound (US) also plays a significant role in diagnosis of DCIS. Gwak et al. [55] conducted a retrospective study of US for detecting DCIS and found that US is more accurate than mammography. In a similar study by Moon et al. [56], DCIS detected by US that has speculated margins, marked hypoechogenicity, thick echogenic margin, and posterior acoustic shadowing is highly suggestive of invasion.

The literature shows that each and every imaging technique available for detecting DCIS has pitfalls and limitations, but each technique also complements one other. Clinicians and radiologists will need to decide which imaging technique is appropriate for their particular patient, taking into consideration her age, family history, and other risk factors. It must be pointed out, however, that MRI is very expensive; in the United States, the average cost of a breast MRI is $5000.00 [57]. For this reason, the indications for preoperative MRI for the diagnosis of breast diseases are clearly stated in the literature and guidelines and ensure that only selected patients undergo breast MRI [58].

Complete physical examination is mandatory after discovery of a possible lesion or lesions on an imaging study; however, the ultimate diagnosis of the lesion still depends on the histology of a biopsy specimen. Currently, the 3 most popular methods of biopsy are needle biopsy, core needle biopsy (CNB), and vacuum-assisted biopsy. Fine-needle aspiration (FNA) is not adequate to establish a diagnosis of DCIS [59]. With advances in imaging, CNB can now be performed as a US-guided or stereotactic procedure by the radiologist. CNB is the best method for establishing the histologic diagnosis of DCIS. Vacuum-assisted biopsy has a high specificity and sensitivity, but may still miss a diagnosis of DCIS in 17% of cases [60].

Prior to image-guided biopsy, needle localization excisional biopsy was a very common practice for treating DCIS. This technique has the advantages of completion of therapy, provided a negative margin is obtained, and is therefore highly cost effective [61]. However, this method is rarely used today for treating DCIS.

Preoperative variables of CNB for diagnosis of DCIS are significantly associated with under-staging of the disease and include experience of the operator, biopsy device, guidance method, size, mammographic features, and palpability of the neoplasm [62]. Based on these variables, 25% of DCIS may have invasive carcinoma and the treatment plan may change. The best approach is to take multiple samples during CNB in order to establish an appropriate histologic diagnosis. CNB specimens must have adequate tissue so that the pathologist can determine the prognostic factors, degree of invasiveness based on nuclear grading, presence or absence of necrosis, mitotic figure, hormonal status of the lesion, and the presence of molecular markers.

5. Pathologic Classification

DCIS is not a single entity, but rather a spectrum of disease; in essence, it refers to malignant change in the ductal epithelium. Because of the heterogenicity of DCIS lesions, no single satisfactory pathological classification system has been adopted. The traditional classification system is based on morphology, architecture, and nuclear grading of the lesion [63], as well as on the presence or absence of necrosis. Silverstein et al. [64] proposed the division of DCIS into 3 groups: high grade, non-high grade with comedonecrosis, and non-high grade without comedonecrosis. One study [65] reported that 23 pathologists were in complete agreement using 5 different classification systems, including that proposed by Silverstein. The International Consensus Conference has failed to endorse any classification, but recommended that pathology reports must include information on nuclear grading, necrosis, polarization, and architectural pattern [66]. Allred [67] proposed the following clarification.

(A) Comedo group—large cell: more aggressive form also referred to as comedocarcinoma.

(B) Noncomedo group—small cell: less aggressive and is further divided into:

  (a) cribriform,
  (b) micropapillary,
  (c) solid.

  DCIS can also be classified depending on the presence of central necrosis [68]:

  (1) DCIS with no central necrosis (noncomedo group).
  (2) Low grade with no central necrosis:
    (a) low grade DCIS,
    (b) intermediate grade DCIS: well differentiated, cribriform, micropapillary, solid- and small-cell type.
  (2) DCIS with central necrosis:
    (a) poorly differentiated,
    (b) comedo type,
    (c) large-cell type.

Such classifications may be clinically meaningful in terms of describing the invasive potential of the neoplasm and informing the treatment plan to avoid overtreatment. In the past, nuclear grading using microscopy could not predict which DCIS would develop into invasive carcinoma. Chapman and colleagues [69] found that nuclear grading by image analysis does have prognostic value, with quantitative nuclear image features able to predict which DCIS will transform into invasive cancer. While the traditional classification is probably going to be changed based on hyperplasia of the duct or epithelium, because an element of subjectivity in the microscopic interpretation of these hyperplastic lesions persists, it is very unlikely that this issue will be resolved soon. A new classification system was proposed based on the presence of mammary intraepithelial neoplasia (MIN) of epithelium either in the duct or lobule, followed by grading in accordance with the trend in many other sites [70]. Most recently, Tavassoli [18] proposed a completely new classification system with some modifications as proposed by Rosai [70]. These classification systems are based on the presence of ductal intraepithelial neoplasia (DIN; Table 1).

Such new classifications have certain advantages and obvious merits, and it is possible that a modified version of the DIN classification will eventually be adopted, though not in the near future. Recently, Costa and Zanini [71] have questioned whether DIN is really a malignant lesion. Guerrieri-Gonzaga and colleagues [72] published their experience in treating 1267 cases of DIN and showed that it is a potentially malignant lesion and should be treated either by BCS or by chemopreventive therapy. These authors have accepted the new pathological classification.

Recently, considerable efforts have been made in evaluating potential molecular markers of DCIS. However, most studies have shown that candidate molecular markers of DCIS have little prognostic value [73, 74]. Approximately 70% of DCIS express ER [75], which is normally expressed by luminal epithelium. Almost 50% of DCIS express HER2/neu [76]. Mutated p53 (a tumor suppressor gene) is expressed by about 25% of DCIS [77]. DCIS of solid, flat or micropapillary type exists in the basal phenotype of breast cancer and demonstrates the same immunophenotype as invasive breast cancer [78]. Androgen receptor (AR) has been detected in female breast cancer and is often associated with apocrine differentiation. Inherited differences in AR CAG length might influence the transition from DCIS to invasive carcinoma, perhaps by modulating the function of AR in breast tissue [79]. All DCIS express E-cadherin, but lobular carcinoma shows focal loss of E-cadherin or complete lack of membrane staining. It is sometimes difficult to differentiate histologically between lobular carcinoma and ductal carcinoma, and E-cadherin immunohistochemical studies can be used to differentiate between the 2 groups of in situ carcinoma of breast [80]. In the future, molecular markers may help to predict which group of DCIS will become invasive carcinoma.

New technologies, such as array-based CGH, RNA expression profiling, have proven to be of great value in distinguishing between poorly differentiated and well-differentiated DCIS by detecting quantitative difference in gene expression. Proteomic analysis also may be able to predict which DCIS will become invasive carcinoma and will help inform the appropriate treatment [81]. Kerlikowske and colleagues [82] conducted standardized pathology reviews and immunohistochemistry staining for ER, PR, Ki67 (tumor proliferating index) antigen, p53, p16, epidermal growth factor receptor-2 (ERBB2, HER2 neu oncoprotein), and cyclooxygenase-2 (COX-2) in paraffin-embedded DCIS tissue. They found that DCIS lesions positive for p16, COX-2, and Ki67, or those detected by palpation are more likely to develop into invasive cancer. Radisky and colleagues [83] examined the significance of p16 INK4a expression in women with atypical hyperplasia and found that expression was not a risk for breast cancer. Most recently, a study by Adler and colleagues [84] found that the vascular pattern is not a predictor of aggressive behavior of DCIS, suggesting that DCIS biology is independent of angiogenesis. We do not yet know whether this also means that vascular endothelial growth factor (VEGF) does not control the aggressive nature of DCIS.

6. Treatment Plan

The goal of DCIS treatment is complete removal of the neoplasm, if possible, and prevention of recurrence. Local treatment of DCIS is simple mastectomy, lumpectomy (though there is usually no lump when DCIS is diagnosed by imaging), lumpectomy with post lumpectomy radiation, quadrantectomy without or with postquadrantectomy adjuvant treatment, followed by chemopreventive therapy. Traditionally, simple mastectomy is the curative treatment for 98% of cases of DCIS, and the local recurrence rate is very low [85]. However, even after simple mastectomy there may be local recurrence. The causes of such local recurrence are either a missed diagnosis of invasive carcinoma during the original surgery or incomplete removal of breast tissue, especially from the skin flap in nipple-sparing mastectomy. Such recurrence occurs only in 1% to 2% of cases [86].

This traditional treatment of DCIS has been challenged by Fisher and colleagues [87] who conducted a randomized trial that demonstrated that total mastectomy and breast conservative surgery for DCIS are associated with equivalent outcomes. Nevertheless, there are certain indications for complete mastectomy for DCIS, beyond the preference of the patient and/or the physician. The indications for total mastectomy as determined by a joint committee of the American College of Surgeons, American College of Radiology, and the American College of Pathologists are women with 2 lesions in the same breast; diffuse malignant appearing lesion in the breast; persistent positive margin after lumpectomy and cavity shaving with multiple attempts; inability to give radiation due to prior radiation or presence of SLE; radiation treatment is not available, especially in underdeveloped countries; extensive DCIS where the tumor is removed with a very small negative margin; tumor size and breast size will produce poor cosmetic result; pregnancy.

Currently, lumpectomy with no radiation in the low-risk patient or with radiation following surgery is the standard of care in the United States and other developed countries

Table 1: Classification of Tavassoli [18].

Proposed classification	Current designation	Necrosis	Excised margin
DIN 1a	IDH	None	Negative
DIN 1b	AIDH, flat monomorphic	−	? Negative
	DCIS, grade 1 (crib/micropap)	−	Positive
	DCIS, grade 2	+	Positive
	(crib/micropap + necrosis or atypia)	+	
	Special type—specify		
DIN 3b	DCIS Grade 3	+ + +	Positive
	(Anaplastic DCIS)	±	

[88]. However, this standard of care is not possible in underdeveloped countries where DCIS is detected by the patient or by the physician as either palpable lump, discharge from nipple, or skin dimpling, rather than by screening or diagnostic imaging studies due to lack of resources [41]. In addition, there are also limited capabilities for radiation treatment following local excision of resectable tumors in developing and underdeveloped countries. Therefore, in these areas, the standard of care is simple mastectomy for all stages of DCIS.

Studies have shown that there is a low recurrence rate of DCIS with excision alone as compared to excision and radiation, especially in low-risk patients [89, 90]. For this reason, it is worthwhile to further explore the possibility of breast conserving surgery alone, especially in patients with low risk. Three randomized trials have compared the outcomes with excision alone versus excision and radiotherapy [91–93]. These trials showed that addition of radiation therapy significantly reduces the risk of recurrence by 40% in the ipsilateral breast. Multiple observational studies, though less powerful than the NSABP-17 trial, also showed lower rates of local recurrence of DCIS or invasive cancer for women undergoing breast conserving surgery followed by radiation, although not all reported statistically significant differences [94–96]. Observational studies from Sweden indicate no mortality benefit associated with breast conserving surgery with radiation compared to breast conserving surgery alone [97]; these results were echoed in one other study [98]. Though these results are from observational studies, taken together, there is no evidence that conservative surgery plus radiation is more or less effective than breast conserving surgery alone. This lack of differential effect can be seen across all of the most important prognostic factors, including grade, tumor size, involved margins, and comedonecrosis.

It is felt that an involved margin is one of the most important prognostic factors for recurrence, yet it is still not agreed what should be the safe margin of lumpectomy [99]. In their review, Revesz and Khan do not provide any specific safe margin; rather, they state that until better data are available, the desirable margin will vary depending on individual factors, including age, histology, and patient preference. It is likely that a safe margin is "ink should not touch the margin of the excised mass and should be at least 2 mm from the surgical margin," as stated by Ruggiero et al. in [42]. The margin varies in the literature, from 1 mm to 3 mm [42]. Blair et al. [100] reported that in the United States, only 48% of surgeons perform cavity and bed shaving, very few undertake frozen section analysis or imprint cytology, and 57% never reexcise with positive margins. The literature suggests that there is still controversy as to whether all patients should be treated with radiation after lumpectomy. Jiveliouk and colleagues [101] recently reported their experiences with the treatment of pure DCIS using lumpectomy and postoperative external beam radiation in an Israeli population; during an 8-year follow-up period, the overall survival, disease-free survival, and event-free survival were 100%, 100%, and 87%, respectively. This is a unique result and may be due to early initiation of treatment or that the biological behavior of DCIS in Israeli women is different from that in women from other Western countries. Kayani and Bhurgri [102] also reviewed their experience with 38 women with DCIS in Karachi, Pakistan; they found that, if untreated, only 40% of cases were aggressive and 60% were very indolent. Most likely, the biological behavior of DCIS is different in Pakistani women such that they do not develop the more aggressive types of DCIS. The Eastern Cooperative Oncology Group recently reviewed their experiences with local excision without radiation for DCIS [103]. Patients with either low or intermediate risk, with tumors measuring 2.5 cm or smaller or high-grade or DCIS 1 cm or smaller who had microscopic margins of 3 mm or wider, were eligible for study. During the 6.2 years of followup, the 5-year rate of cancer recurrence and related morbidity was 6.1% in patients with low or intermediaterisk, and 15.3% in the high-grade DCIS group. This study proves that all patients with DCIS do not need radiation after lumpectomy. Very recently, similar study has been carried out by Ruggiero et al. [42] in 161 patients who were followed for 5 years; the recurrence rate was 6.2% in the group of patients who had only quadrantectomy without radiation therapy. According to these authors, the risk factors for local recurrence were age <45 years, positive margin <2 mm, and grade 3 neoplasm. Based on their findings, the authors recommended adjuvant radiotherapy in patients who had these risk factors for local recurrence.

Taken together, the current trend is that only high-risk patient should undergo adjuvant radiotherapy after lumpectomy. Typically, 50 Gy of external beam radiation is administered in 25 fractions. There is also growing interest in balloon brachytherapy for treatment of DCIS following

lumpectomy, which would allow for accelerated breast radiation therapy. The literature contains reports of satisfactory results with balloon brachytherapy in DCIS in terms of disease-free survival and cosmoses [104, 105]. However, a recent report about the long-term result of brachytherapy for treatment of DCIS was presented at the San Antonio Breast Cancer Symposium (2011) and published by the American Association for Cancer Research [106]. In this study, Smith et al. at MD Anderson Cancer Center reviewed the medical records of 130,535 patients who underwent brachytherapy for DCIS and then were followed for 5 years. Surprisingly, 50% of the patients eventually underwent complete mastectomy, either due to complications of the brachytherapy or recurrence of the tumor. Multiple studies have demonstrated that MRI detects multiple foci in 10%–30% of patients with DCIS, and that neither mammography nor US can detect these metacentric lesions [107]. When these patients are treated with balloon brachytherapy, they are inadequately treated; this may explain why there is such a high recurrence rate of DCIS after brachytherapy. It is therefore appropriate that patients undergo MRI evaluation prior to brachytherapy, and if multiple foci are present, then either these patients should undergo total mastectomy or total breast radiation.

Controversy exists regarding the treatment of micrometastasis in DCIS. Micrometastasis should be treated either with axillary dissection, chemotherapy, or radiotherapy [108]. DCIS is a part of breast and ovarian cancer syndrome [109], and the BRCA1 and BRCA2 mutation rate in invasive carcinoma is same as that in DCIS. These findings suggest that a patient with personal and family history of breast cancer and or ovarian cancer should be followed very closely as per the risk protocol for breast cancer.

The value of genetic testing for BRCA1 and BRCA 2 mutation is its ability to reduce the number of women who develop breast cancer and the number of women who die of disease. Patients with BRCA1 and BRCA2 mutations have several options for breast cancer prevention. These options include prophylactic total mastectomy, prophylactic bilateral oophorectomy and chemoprevention with SERM, third generation aromatase inhibitors, or raloxifene. Statistical analyses indicate that total mastectomy reduces the risk of developing breast cancer by 89% [110]. Though prophylactic total mastectomy offers the best protection against developing breast cancer in BRCA1 and BRCA 2 mutation carriers, one study in Canada showed that the majority of women with BRCA1/2 mutations are unwilling to undergo such a radical surgical procedure [111].

The NSABP-24 trial assessed the value of tamoxifen following the diagnosis of DCIS and found that treatment reduces the recurrence rate of DCIS or invasive carcinoma in the ipsilateral breast. The effect of tamoxifen is highly significant for patients with ER+ DCIS, whereas the effect in reducing recurrence DCIS in the ipsilateral breast is not significant in ER− DCIS [112]. The same trial also found that tamoxifen therapy was associated with a 50% reduction of DCIS or invasive carcinoma in the contralateral breast, but had no impact on all-cause mortality. Combined treatment (lumpectomy, radiation, and tamoxifen) compared with lumpectomy and tamoxifen reduced the overall rate of cancer 29% [113]. This study also showed that tamoxifen is less effective in patients without comedonecrosis or who have smaller tumors. The unwanted effects of tamoxifen include hot flashes, fluid retention, vaginal discharge, osteoporosis, thromboembolic disease, and endometrial carcinoma. A study by Cuzick and colleagues [114] reported that the risk reduction of breast cancer with tamoxifen persists for at least 10 years, but that most side effects do not continue after 5 years. However, an observational study by Warren and colleagues [115] found that women with DCIS who receive tamoxifen had the same hazard of local recurrence of DCIS or invasive cancer as women who did not receive tamoxifen.

In addition to tamoxifen, other SERMs such as raloxifene and lasofoxifene are also used as chemoprevention agents. The STAR trial, MORE trial, and CORE trial have studied the role of raloxifene for prevention of breast cancer and have shown positive results [116]. However, a recent study by Viring and colleagues [117] reported that while raloxifene reduced the risk of invasive breast cancer, it was not associated with decreased incidence of DCIS.

Currently, third-generation aromatase inhibitors (anastrozole, letrozole, and exemestane) are also used as chemoprevention agents with greater specificity and fewer side effects [118]. However, all of these chemopreventive drugs have no impact on ER-tumors and this remains a challenging area for breast cancer prevention. Possible agents for prevention of ER-neoplasms include cyclooxygenase-2 inhibitors, statins, and vitamin D analogs. Yet none of these drugs has been tested in humans in a randomized controlled trial, which is necessary to prove the efficacy of these drugs for prevention of breast cancer. There is one laboratory study in progress that is evaluating inhibition of p38 kinase as a chemopreventive measure for ER-breast tumors [119]. The p38 kinase causes cell proliferation, and most ER-negative breast neoplasms overexpress p38 kinase. This preliminary study will provide the foundation for new approaches to the treatment or prevention of ER-breast neoplasms.

Rexinoid LG100268 [120] has been shown in animal models to be an effective chemopreventive agent for prevention of preinvasive neoplasm of the breast with minimal toxicity [121]. Future trials are needed in humans to assess the clinical translation of this chemopreventive agent. PPAR-α and PPAR-γ ligands induce apoptotic and antiproliferative responses, respectively, in human breast cancer cells, and their activation is associated with specific changes in gene expression [122]. Therefore, PPAR-selective retinoids may also be potential chemopreventive agents.

The issue of sentinel lymph node (SLN) biopsy in DCS has been extensively studied by various investigators. Tada and colleagues [123] have found that the incidence of positive SLN is 1.25% and 6.8% in DCIS and intraductal carcinoma (IDC), respectively. Intra et al. [124] studied the incidence of positive SLN in 854 patients with DCIS. They found the incidence of positive SLN was 4%, or 12 cases. Of these 12 cases, 7 had micrometastases with tumor size <2 mm and 5 had macrometastases with tumor size >2 mm. Four additional cases had isolated tumor cells (ITC). Julian and colleagues [125] reviewed the records of 813 patients

with DCIS. These patients were studied under the auspices of the NSABP B-17 and B-24 projects. The NSABP B-17 investigators found that 7 patients developed ipsilateral nodal recurrence (INR) and the overall INR rate was 0.83 per 1000 patient-years. In NSABP B-24, the overall INR rate was 0.36 per 1000 patient-years. It was concluded that INR can be considered a surrogate for axillary involvement at the time of diagnosis of DCIS. These findings suggest that the rate of positive SLN in DCIS is so low that there is generally no indication for performing SLN biopsies in patients with DCIS. However, if at any time the patient undergoes complete mastectomy, then the patient must also have an SLN biopsy. Other relative indications of SLN biopsy are perineural invasion and high grade with comedonecrosis.

Various treatment options should be discussed with the patient with DCIS. Patients should be told in detail about the biological behavior of the DCIS, with special reference to the natural history of the disease, the outcomes of various types of treatment, the recurrence rate after treatment, the results of salvage treatment in the event of recurrence, the risks and benefits of the various treatment options, and the disease-free survival and overall survival rates of the various treatments. The patient and possibly family members should be actively involved in treatment decision making. Katz and colleagues [126, 127] conducted a population-based cohort study of 659 women from the Detroit and Los Angeles areas who were diagnosed with DCIS in 2002 to examine the role of the patient in treatment decision making and how the patient's input affected the treatment. In the study, greater patient involvement in the decision-making process led to larger number of mastectomies. Furthermore, the Katz study showed that only 13.1% of women were not influenced by their physicians concerns about recurrence and underwent mastectomy compared to 48.5% who were greatly influenced by the possibility of recurrence. This finding suggests that the engagement of a knowledgeable surgeon in the treatment discussion can be a very powerful tool in guiding the treatment of a particular patient. The surgeon must consider all the risk factors of recurrence after the definitive curative treatment of DCIS and must work with the oncologist to select adjuvant treatment, if needed, and chemopreventive treatment.

7. Conclusion

DCIS is a heterogeneous neoplasm whose biological behavior is still incompletely understood. Epidemiologic studies show that with the advent of various imaging techniques, the incidence of DCIS increased and has reached a plateau in past decade. Approximately 80% of DCIS cases are diagnosed by imaging studies in developing countries, whereas the majority of cases in developing or underdeveloped countries present as palpable lumps, nipple discharge, and comedonecrosis. Each of the imaging modalities has advantages and limitation, but they can complement each other to achieve an accurate diagnosis of DCIS. Definite histological diagnosis of nonpalpable DCIS is established by either needle- or US-guided CNB or stereotactic biopsy or vacuum-assisted biopsy. Currently, CNB is best technique to obtain an accurate histologic diagnosis. Various treatment options are available. The gold standard of treatment of DCIS in developed countries is wide local excision of the tumor with negative margins followed by external beam radiation. Such treatment options may not be available in underdeveloped countries, where total mastectomy is the treatment of choice. Surgery and radiation are superior to surgery alone with regard to recurrence, but there is no benefit in terms of overall survival for either of these approaches. Long-term survival is possible, even in underdeveloped countries without treatment. Additional research is needed to determine the role of balloon brachytherapy as an adjuvant treatment. Tamoxifen is a beneficial adjuvant therapy. Further research to understand the biological nature DCIS will resolve some of the remaining controversy about the best treatment for DCIS. Various preventive measures are available to protect against the development or progression of DCIS, including surgical and nonsurgical interventions. Investigations are ongoing regarding molecularly targeted drug development for prevention and treatment of DCIS.

Conflict of Interests

The author declares no conflict of interests.

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Review Article

Ductal Carcinoma In Situ of the Breast

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Ductal carcinoma in situ (DCIS) of the breast represents a complex, heterogeneous pathologic condition in which malignant epithelial cells are confined within the ducts of the breast without evidence of invasion. The increased use of screening mammography has led to a significant shift in the diagnosis of DCIS, accounting for approximately 27% of all newly diagnosed cases of breast cancer in 2011, with an overall increase in incidence. As the incidence of DCIS increases, the treatment options continue to evolve. Consistent pathologic evaluation is crucial in optimizing treatment recommendations. Surgical treatment options include breast-conserving surgery (BCS) and mastectomy. Postoperative radiation therapy in combination with breast-conserving surgery is considered the standard of care with demonstrated decrease in local recurrence with the addition of radiation therapy. The role of endocrine therapy is currently being evaluated. The optimization of diagnostic imaging, treatment with regard to pathological risk assessment, and the role of partial breast irradiation continue to evolve.

1. Introduction

Ductal carcinoma in situ (DCIS) of the breast is a complex pathologic entity in which malignant cells arise and proliferate within the breast ducts without invasion of the basement membrane. The increased use of screening mammography has led to a significant increase in the diagnosis of earlier stage breast cancers, including ductal carcinoma in situ. According to the Surveillance Epidemiology and End Results program (SEER) from 1975–2008, in situ breast cancers represented approximately 15% of all new breast cancer diagnoses in the United States [1]. DCIS consists of approximately 84% of all in situ disease, with lobular carcinoma in situ (LCIS) forming the bulk of the remainder. DCIS will account for approximately 27% of all newly diagnosed breast cancers or 77,795 new cases estimated in 2011 [2]. The age-adjusted DCIS incidence had increased an average of 3.9% annually from 1973 to 1983 and approximately 15% annually from 1983 to 2008 [3]. Since 2003, the incidence of DCIS has declined in women aged 50 years and older, while the incidence continues to increase in women younger than age 50 [4]. Overall, the rate of increase in incidence has been higher for DCIS than for any other type of breast cancer. As the incidence of DCIS increases, the treatment options continue to evolve.

In the past, DCIS was an uncommon disease that was routinely treated with mastectomy. However, with the increasing acceptance of breast conservation therapy for invasive breast cancers, initial attempts at breast-conserving surgery have also indicated a potentially acceptable treatment modality for DCIS [5]. Currently, several studies have shown breast conservation therapy to be effective for the management of DCIS. In 1983, 71% of cases were treated by mastectomy in contrast to only 33% in 2007 [6]. Today, mastectomy, lumpectomy followed by radiation therapy, and lumpectomy alone have all been advocated as management strategies for DCIS. Treatment selection for the individual patient with DCIS requires a clinical, mammographic, and pathological evaluation. A large proportion of women diagnosed with DCIS today are candidates for breast conservation, with relatively few absolute or relative contraindications due to toxicity concerns. With improvements in modern breast reconstructive techniques, mastectomy may be a more appealing alternative for individuals with anticipated poor

cosmetic outcome as a result of breast-conserving surgery and radiation therapy. One factor affecting cosmesis may include a large surgical defect required to attain negative margins. Prior to the determination of a patient's suitability for breast-conserving therapy, a thorough evaluation to determine the extent and characteristics of the patient's disease is necessary. Patient preference will also play a role in the final treatment decision. We present this paper as an update to our previous review in 2009 [7].

2. Patient Evaluation

An adequate history and physical examination with evaluation of the patient's overall health should be performed. History assessment should include a personal or family history of malignancy, a breast cancer risk assessment including previous breast biopsies, history of abnormal mammograms, and the use of hormone replacement therapy or oral contraceptives. Other factors include nulliparity or late age at first birth, late menopause, and obesity in postmenopausal women [4]. Physical examination should document tumor size and location if palpable, nipple appearance, and the presence of nipple discharge. A thorough examination of the opposite breast and bilateral axilla should clinically confirm limited disease. The overall breast size and configuration should be taken into consideration for assessment of treatment options.

In the past, most DCIS had presented as a palpable mass. Now, less than 10% of disease is palpable, with an abnormality found radiographically as the most common presentation and is found in approximately 20% of all screening mammograms [8]. DCIS may also present as pathologic nipple discharge with or without a mass or may be identified incidentally in a breast biopsy performed to treat or diagnose another abnormality. Patients who present with a palpable mass have a significantly higher potential for occult invasion, multicentricity, and local recurrence, than those who present with nonpalpable lesions [9, 10]. If left untreated, invasive breast cancer may develop in 30–50% of DCIS [11, 12]. The anatomic location of DCIS within the breast is not significantly different than invasive carcinoma. Most tumors were found in the upper outer quadrant (43.9%), then in the upper inner quadrant (9.0%), in the central quadrant (8.5%), in the lower outer quadrant (8.1%), and finally in the lower inner quadrant (6.9%) [13]. DCIS is rarely multicentric with radiologic and pathologic correlative studies of mastectomy specimens in patients with DCIS indicating only one multicentric lesion out of 82 mastectomy specimens [14].

3. Radiographic Evaluation

DCIS commonly appears as clustered microcalcifications, although a nonpalpable mass may also represent DCIS. Calcifications are typically pleomorphic, varying in size, form, and density, and are grouped in segmental or linear arrangements reflecting their presence in the duct [15] (Figure 1). In contrast, calcifications associated with benign disease tend to be more rounded and uniform in density.

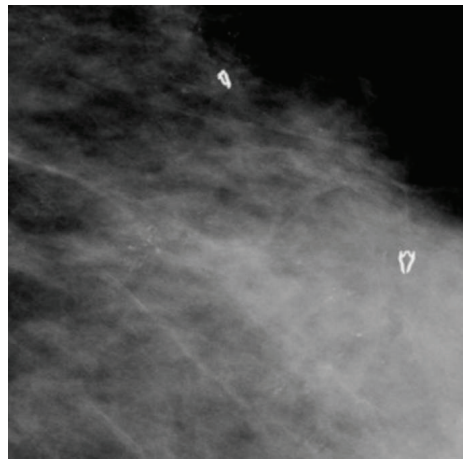


Figure 1: Mediolateral oblique projection of dystrophic branched calcifications.

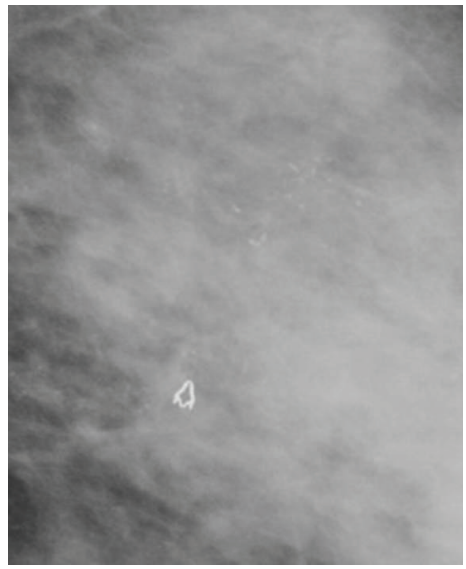


Figure 2: Craniocaudal view of calcifications with irregular shape and form.

Magnification views help delineate the presence and extent of microcalcifications (Figures 2 and 3).

The entire breast should be carefully examined to determine if areas of suspicion are present elsewhere in the breast. Mammography alone may underestimate the extent of disease. This is increasingly likely with larger lesions. Screening mammogram has an overall sensitivity of 55–86% [8, 16]. In a review of mammographically detected DCIS, 72% presented as calcifications and 12% presented as calcifications with an associated soft tissue abnormality [17]. Of malignant appearing microcalcifications, 92% are associated with a malignant histologic diagnosis [18]. All patients should have a mammogram performed before resection, and selected patients should have a mammogram performed after resection, in order to ensure the completeness of

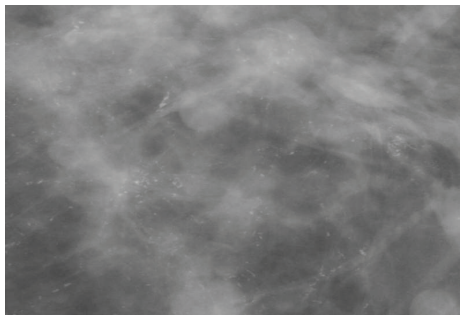


Figure 3: Extensive irregular pleomorphic calcifications with an underlying density.

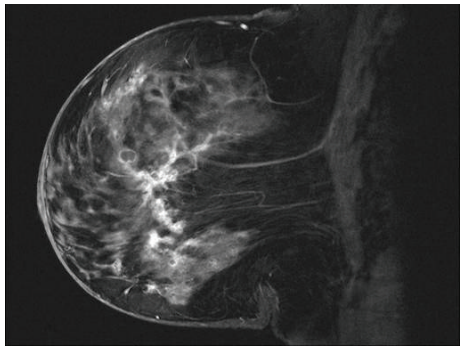


Figure 4: Abnormal enhancement of the ductal system.

resection. Specimen radiography is helpful and may be performed routinely.

Breast MRI is currently being evaluated in DCIS. MRI has shown to be highly sensitive in the detection of invasive disease, with sensitivities ranging from 89–99%, but the sensitivity of MRI detection for DCIS is much lower, ranging from 40–80% [19]. Additionally, MRI can both under- and overestimate involvement, from 11–25% and 11–28%, respectively [20, 21]. In a multicenter study, the combination of mammography and MRI imaging has been shown to detect 82% of invasive lesions, but evaluation of the same dataset for DCIS showed that the combination of modalities was only able to detect 46% of DCIS due to a high false negative rate [19, 21]. This was still higher than the mammography alone detection rate of 35%. The increased sensitivity in the detection of occult multifocality and/or extensive residual disease [22–24] may help to guide local management decisions. Increased detection of breast abnormalities after MRI may alter the treatment management decision, with a change in treatment management in up to 15–28% of cases [21, 25].

The pattern of enhancement of DCIS in MRI can be variable including both ductal and regional enhancement (Figure 4). Ductal enhancement accounted for 21% of MRI detected lesions and 59% of 150 nonmass lesions [26]. Further study is currently underway to determine the optimal breast MRI technique for the identification of DCIS and to refine the histopathologic correlation [22, 24].

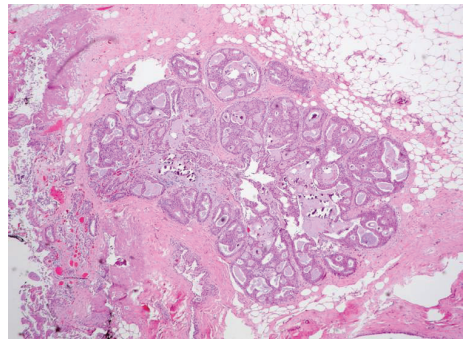


Figure 5: Low grade cribriform DCIS with associated microcalcifications.

4. Diagnosis

As the majority of DCIS does not present with a palpable mass, image-directed procedures are necessary for diagnosis and treatment. Ultrasound-guided biopsy is useful for nonpalpable masses but usually cannot be relied upon for biopsy of microcalcifications. Stereotactic core needle biopsy may be used as the initial approach for biopsy of suspicious nonpalpable mammographic abnormalities with a sensitivity of 85–97% and a specificity approaching 100%. For the evaluation of microcalcifications, vacuum-assisted biopsy (VAB) is an even more accurate technique than core biopsy [27–29]. When possible, multiple cores should be taken and specimen radiography performed to confirm an adequate sampling of the abnormality. VAB is a reliable method to diagnose nonpalpable DCIS with a low underestimation rate and a false negative rate similar to that of open surgical biopsy [30]. Sensitivity and negative predictive value have been reported to be greater than 99% with VAB [27]. Open surgical biopsy is preferred if the abnormalities are not amenable to stereotactic breast biopsy or ultrasound-guided biopsy. For small lesions likely to be completely removed with the diagnostic biopsy, a marker should be left at the biopsy site for localization of the area. If a diagnosis of DCIS is made by percutaneous core needle biopsy, areas of invasion may be found in up to 20% of cases at the time of surgical excision [31].

5. Pathology

DCIS is a heterogeneous entity with several morphologic variants that is thought to be part of a spectrum of proliferative ductal lesions of the breast that extend from epithelial hyperplasia without atypia to microinvasive carcinoma. DCIS had historically been classified primarily by architectural pattern into comedo, cribriform, papillary, micropapillary, and solid subtypes (several examples are seen in Figures 5, 6, 7, and 8). With the increasing use of breast conservation therapy, there is a need to identify those lesions more likely to recur or progress to invasive cancer, which are thought to correlate with tumors with higher nuclear grade and the presence of comedo necrosis [32]. More recently, there is a push to convert the designation of ductal carcinoma

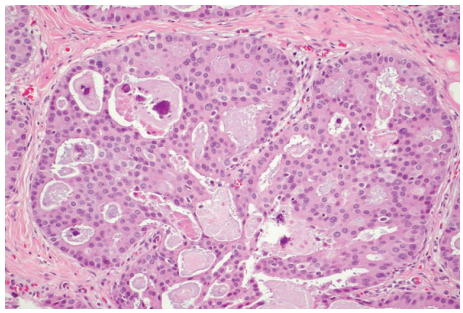


Figure 6: Cribriform DCIS with calcifications under high power magnification. Uniform even cell placement, central necrosis, and associated calcifications are seen.

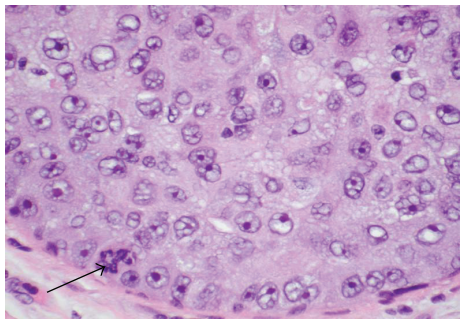


Figure 7: High-grade DCIS with atypical pleomorphic nuclei and prominent nucleoli seen under high power magnification. Bizarre (tripolar) mitotic figure at bottom left (arrow).

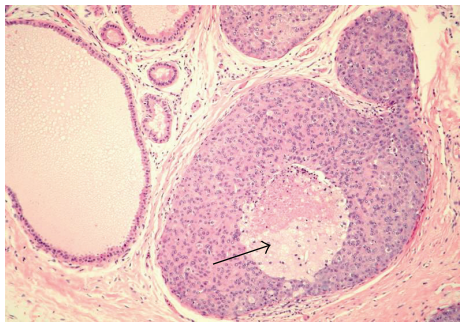


Figure 8: Solid DCIS with central necrosis (arrow). Adjacent benign ducts are shown for comparison.

in situ to ductal intraepithelial neoplasia (DIN), similar to cervix cancer, although this has not been widely accepted [33].

The assessment of surgical margins is the most important detail in the pathologic evaluation of DCIS in patients under consideration for breast conservation. The definitions of positive and negative margins vary; however, microscopic extension to the surgical margin warrants further surgery [34]. Studies have shown that margins less than 1 mm show significant risk of recurrence [35], while there may not be additional benefit with a margin greater than 2 mm [36]. The pathologist should clearly specify whether DCIS is transected at the surgical margin and report the distance of the closest margin.

6. Management of the Axilla

The incidence of lymph node metastases in DCIS is low, occurring in less than 1-2% of patients with DCIS [37] and is likely due to the presence of unrecognized invasive cancer [38]. The risk of finding occult invasive disease depends on how the cancer presented and on how the lesion was sampled. Although it is uncommon, DCIS may present as a palpable mass in up to 10% of all cases. These palpable DCIS may harbor invasive disease in up to 26% of cases. Further, when mastectomy is needed to treat the DCIS due to extensive calcifications throughout the breast, the risk of finding occult invasive disease is reported to be as high as 28%. Routine use of core needle biopsy has been found to be accurate in diagnosing DCIS. However, sampling error may occur resulting in missed invasive disease in 10–20% of women [39–41]. Based on these data, the decision for axillary evaluation, specifically sentinel lymph node biopsy (SLNB), must be determined on an individual basis depending on the suspected risk of finding invasive disease at the time of final pathologic assessment of the surgical specimen. A recent review of axillary surgery practices in patients with DCIS evaluated 2159 women of whom 470 (22%) with high risk features completed a SLNB [42]. Of these, 43 were found to have a positive SLNB. When the sizes of the SLN metastases were evaluated, only 7 were larger than 0.2 mm. The remaining positive lymph nodes had only isolated tumor cells within the sentinel node. The authors conclude that a need for SLNB in the setting of DCIS exists but only in cases where high risk features are present and the risk of sampling error is significant. In practice, SLNB for DCIS is generally performed only when DCIS presents as a palpable mass or when mastectomy is being performed.

7. Selection of Treatment

While no prospective randomized trial exists comparing mastectomy, breast conservation with radiation, and breast conservation without radiation for the treatment of DCIS, retrospective data suggest survival is similar among all methods and ranges between 98–100% [43, 44]. From this, it is accepted that treating DCIS is therefore not about survival but instead about limiting the rate of local recurrence. A multidisciplinary approach to DCIS is necessary for optimal patient evaluation and allows all data to be integrated in order to make clear treatment recommendations. Patient preference should also be factored into the treatment decision.

Historical data demonstrates the risk of local recurrence after mastectomy is extremely low (<1%) (Table 1). Therefore, it remains an option for women who are not interested in or who have contraindications to breast conservation therapy. It is accepted as a standard therapy for DCIS but has been criticized based on the irony that an in situ disease that does not influence survival may be treated in some cases with a more radical surgical approach.

Table 1: Results of treatment of DCIS with mastectomy.

Study	Number of patients	Followup (months)	Number of recurrences
Sunshine et al. [45]	68	120	0
Farrow [46]	181	60	2
Silverstein et al. [47]	228	84	2
Kinne et al. [48]	101	138	1
Schuh et al. [49]	51	66	1
Arnesson et al. [5]	28	77	0

Nonetheless, absolute and relative contraindications to breast conservation exist and include women in whom complete surgical clearance of tumor would result in unacceptable cosmesis, diffuse microcalcifications throughout the breast, the presence of a contraindication to radiation therapy, and patient preference.

8. Breast Conservation Therapy

When breast conservation is appropriate, the goals of the surgical procedure are total removal of the suspicious or known malignancy with minimal cosmetic deformity. Oncoplastic surgery, combining principles of oncologic surgery with plastic surgery techniques, has helped advance surgical excision of larger volumes of tissue, maintaining, oncologic principles while maintaining and sometimes improving cosmetic outcome [50].

The Early Breast Cancer Trialists Collaborative Group (EBCTCG) recently published a meta-analysis and overview of the DCIS prospective randomized trials treating women with breast-conserving surgery with or without radiation therapy [51]. The data continue to demonstrate no survival benefit from radiation therapy. However, it also continues to demonstrate the significant impact of radiation therapy in reducing local recurrence after breast-conserving surgery by 50–60%. Although lumpectomy alone is an accepted treatment for DCIS, rates of local recurrence are approximately 3% per year while the addition of radiation reduces this risk to approximately 1-2% per year. Interestingly, whether radiation therapy is given or not, 50% or more of all local recurrences after BCS for DCIS are invasive recurrences with recurrent DCIS making up the remainder. In depth analysis of the local recurrences in NSABP B-17 and B-24 by Wapnir et al. finds that mortality rates are significantly higher in women with a local recurrence of invasive breast cancer after BCS for DCIS [52].

The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-17 trial is the first randomized, controlled trial for DCIS which confirmed the effectiveness of RT in decreasing local recurrence after lumpectomy with negative resection margins in mammographically or clinically detected DCIS [52–55] (Figure 9).

The updated analysis with 15-year followup showed a decreased cumulative incidence of both invasive and noninvasive ipsilateral breast recurrences from 35% to 19.8% with the addition of radiation therapy. The incidence of invasive ipsilateral breast recurrence was also decreased from 19.4 to 8.9% with the addition of radiation therapy to lumpectomy [52] (Table 2). In the NSABP B-17, the annual mortality rate due to breast cancer in patients who had breast-conserving therapy was 0.67%.

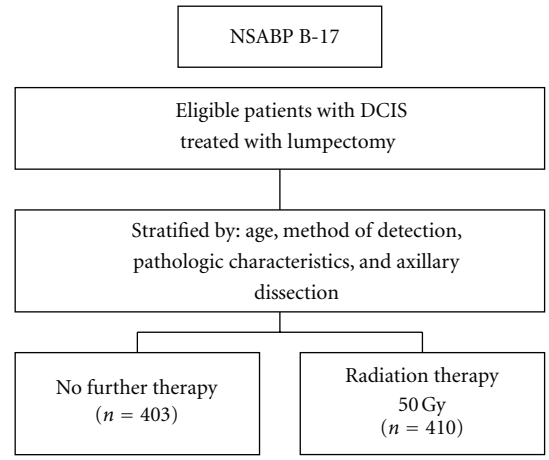


Figure 9: Diagram of NSABP-B17 trial.

As confirmed by randomized trials, breast conservation including radiation therapy remains a standard treatment option for women diagnosed with DCIS (Table 3). Despite the results of randomized trials indicating the benefit of radiation therapy after conservative surgery, questions remain regarding the identification of a subgroup of patients who may not require radiation therapy after wide local excision.

The idea that some subgroups of women with DCIS may be appropriately treated without radiation therapy has been considered for well over a decade. Retrospective data, especially those of Silverstein et al. [35], have supported this hypothesis advocating that patients with a surgical margin of greater than 10 mm may be spared radiation with no change in their risk of local recurrence. More contemporary data published by Rudloff et al. [62] appears to support this as well, suggesting that there is no additional benefit to radiation therapy in patients with a margin >10 mm. Other published experiences have demonstrated variable recurrence rates with local excision alone (Table 4).

To date, prospective data have failed to validate the elimination of radiation therapy from the treatment plan of women completing BCS for DCIS. Two prospective trials have attempted to identify a subset of patients with low-risk DCIS who may not benefit from the addition of radiation therapy following a local excision. One trial prospectively enrolled 158 patients with low-to-intermediate grade (LIG) DCIS with lesions ≤2.5 cm to treatment with a wide local excision with margins ≥1 cm followed by observation. This trial was closed to accrual after stopping criteria were met. With a median follow-up time of 40 months, 13 patients (8%) had developed a local recurrence [65]. The Eastern Cooperative Oncology Group (ECOG 5194) and the North Central Cancer Treatment Group (NCCTG) conducted a single-arm prospective study with 670 patients with either LIG DCIS measuring ≤2.5 cm or high-grade (HG) DCIS,

Table 2: NSABP B17: ipsilateral breast tumor recurrence.

NSABP B-17	Number of events	Rate/1000 patient/year	Relative risk	*P* value
Noninvasive				
Lumpectomy alone	62	14.7	0.47	<0.001
Lumpectomy + RT	37	7.5		
Invasive				
Lumpectomy alone	79	18.8	0.52	<0.001
Lumpectomy + RT	44	9.0		

Table 3: Results of treatment after breast-conserving therapy for DCIS.

Study	Number of patients	Followup (months)	Number of recurrences (%)
Kurtz et al. [56]	44	61	3 (7)
Kuske et al. [57]	70	48	3 (4)
Silverstein et al. [58]	103	45	10 (10)
Solin et al. [59]	268	124	45 (17)
B17, Wapnir et al. [52]	410	207	81 (20)
B24, Wapnir et al. [52]	900	163	149 (17)
Bijker et al. [60]	507	126	75 (15)
UKCCR [61]	267	53	15 (6)

Table 4: Results of DCIS treated with excision alone.

Study	Number of patients	Followup (months)	Number of recurrences (%)
Lagios et al. [63]	79	44	8 (10)
Silverstein et al. [58]	26	18	2 (8)
Schwartz et al. [64]	72	47	11 (15)
B17, Wapnir et al. [52]	403	207	141 (35)
Bijker et al. [60]	503	126	132 (26)
UKCCR [61]	544	53	97 (18)

measuring ≤1 cm who had microscopic margin widths of ≥3 mm and no residual calcifications on postoperative mammograms to determine the risk of ipsilateral breast events in patients with DCIS with local excision alone. A total of 670 patients enrolled were eligible for analysis. Patients enrolled in the year 2000 and later had the option to take tamoxifen. The 5-year rate of ipsilateral breast events in the LIG group was 6.1%, while the 5-year incidence for the HG group was 15.3% [66].

In comparison, Motwani et al. performed a retrospective review on 263 patients who met the eligibility criteria of the ECOG 5194 study and underwent breast-conserving surgery with or without adjuvant radiation. Five-year and 7-year ipsilateral breast tumor recurrence (IBTR) for the LIG cohort was 1.5% and 4.4% for patients treated with adjuvant radiation compared with the 6.1% and 10.5% with breast-conserving surgery alone, respectively. The 5-year and 7-year IBTR for the HG cohort was 2.0% and 2.0% with adjuvant radiation compared with 15.3% and 18% with breast-conserving surgery alone, respectively [67].

To further clarify the role of radiation therapy following excision in patients with low risk DCIS, RTOG recently completed RTOG 98-04, a trial randomizing low-risk DCIS patients to breast-conserving surgery with or without adjuvant radiation therapy (Figure 10). Initial results for RTOG 98-04 were reported in 2011, which included a subset of women with mammographically detected LIG DCIS, size ≤2.5 cm, and margins ≥3 mm. Tamoxifen use for 5 years was allowed but not required. Monthly accrual numbers were not met, therefore the study was closed early. A total of 593 women were randomized to breast-conserving surgery followed by whole breast radiation totaling 5000 cGy or to observation. The median followup was 6.46 years. Local failure at 5 years was 0.4% for women treated with radiation versus 3.2% of women who were observed ($P = 0.0023$). Size, grade, margin status, and age had no impact on local failure. In the observation arm, local failure with tamoxifen was 3% versus 8.9% without tamoxifen. Contralateral breast failures were similar in both arms at 3.6% with tamoxifen use and 2.7% without. Both regimens were well tolerated and the disease-free survival and overall survival were not different between the two arms. The local failure rate of 3% compared favorably with the 6.1% local failure at 5 years in the ECOG 5194 observation trial, which may reflect the increased use of tamoxifen. In the future, clinical trials for this subset of women may include endpoints, such as, acute and chronic sequelae of local and systemic therapy, assessment of cosmetic results, and the economic impact of the cost of therapy. Inclusion of these data may allow us to better inform this subset of patients about the risks and benefits of adjuvant therapies.

9. Hypofractionation

Hypofractionation has been investigated extensively for invasive carcinoma but whether hypofractionation is as effective for pure DCIS has yet to be established. In a retrospective review, Wai et al. found hypofractionation to be as effective as standard fractionation [68]. The Trans Tasman Radiation Oncology Group (TROG) has recently initiated a prospective international clinical trial randomizing patients with pure DCIS to hypofractionated versus standard fractionated whole breast RT, with or without a partial breast boost.

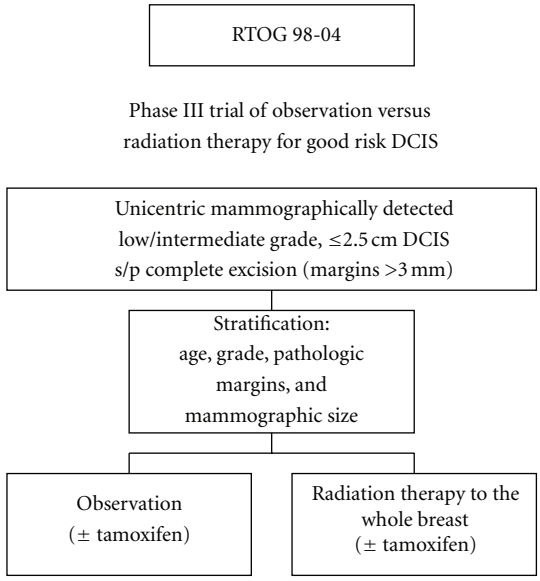


Figure 10: Diagram of RTOG 98-04 trial.

Table 5: Initial recurrence rates after partial breast irradiation for DCIS.

Study	Number of patients	Followup (months)	Number of recurrences
Benitez et al. [72]	100	9.5	2 (2%)
Chao et al. [73]	23	22.1	1 (4%)
Jeruss et al. [74]	194	54.4	7 (3.6%)
Benitez et al. [75]	36	66.0	0 (0%)

10. Partial Breast Irradiation

The majority of local breast tumor recurrences occurs in proximity to the original primary tumor site [69, 70]. In addition, the incidence of local recurrences elsewhere in the breast is equivalent in women treated with or without radiation therapy after a lumpectomy [71]. As a result, there is increasing interest in partial breast irradiation techniques to treat the lumpectomy cavity alone with radiation as opposed to whole breast radiation. Early experience with partial breast irradiation in patients with DCIS suggests outcomes similar to conventional whole breast radiation therapy (Table 5).

Partial breast irradiation can be delivered through multiple techniques, including multicatheter brachytherapy, intracavity brachytherapy, partial breast external beam radiation therapy, or intraoperative radiation. The typical treatment course for brachytherapy and external beam therapy consists of 3400 cGy in 10 fractions or 3850 cGy in 10 fractions delivered twice a day. Intraoperative radiation is typically delivered in 1 dose of 1000–2000 cGy.

The NSABP is currently conducting a randomized, Phase III trial, B-39, to test the equivalency of partial breast irradiation by randomizing patients with Stage 0-II breast cancer status after a lumpectomy to whole breast radiation or partial breast radiation (Figure 11). Until NSABP B-39 has completed accrual and follow-up results are available, physicians are encouraged to use caution in selecting appropriate patients for partial breast irradiation and discuss the potential uncertainties with this technique. The American Society for Therapeutic Radiology and Oncology (ASTRO) has published consensus guidelines for treatment of patients outside of clinical trials [76].

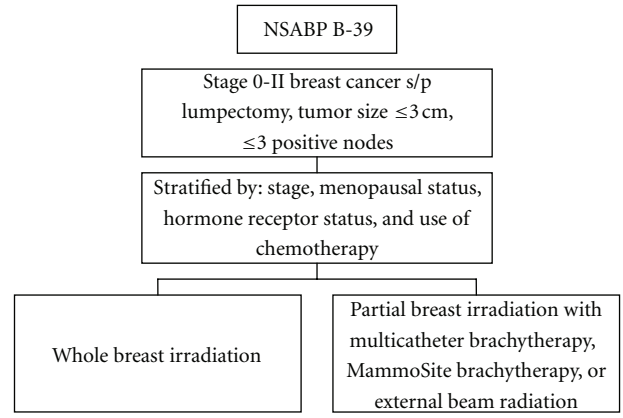


Figure 11: Diagram of NSABP B-39 trial.

11. Oncotype DX

Recently, Solin performed a prospective validation study using the Oncotype DX assay on DCIS tumor specimens from 327 patients from ECOG 5194. Their results were presented at the San Antonio Breast Cancer Symposium, validating that this multigene assay quantifies recurrence risk and complements traditional clinical and pathologic factors in selected patients with DCIS treated with surgical excision without adjuvant radiation [77]. This provides us with a new tool to help predict women at higher risk for local recurrence, but further evaluation is necessary to see how it will be incorporated into practice.

12. Endocrine Therapy

The NSABP has conducted a double-blind randomized, controlled trial, NSABP B-24, to examine the potential benefit of tamoxifen in patients with DCIS who were treated with lumpectomy and radiation therapy [78] (Figure 12). Women were randomized to either tamoxifen or placebo for 5 years following breast-conserving therapy. With 15-year followup, tamoxifen reduced the risk of ipsilateral invasive breast tumor recurrence by 32% in patients treated with excision plus radiation therapy [55]. Noninvasive ipsilateral breast recurrence was a nonsignificant 16% reduction in risk. Tamoxifen also reduced the risk of contralateral breast cancer development by 32%. No differences in distant disease, breast-cancer-specific survival, or overall survival were found between those patients treated with or without tamoxifen. Tamoxifen can cause life-altering side effects, such as, thromboembolic disease and uterine cancer and is not without potential serious toxicity. The role of tamoxifen in the treatment of patients with DCIS remains uncertain.

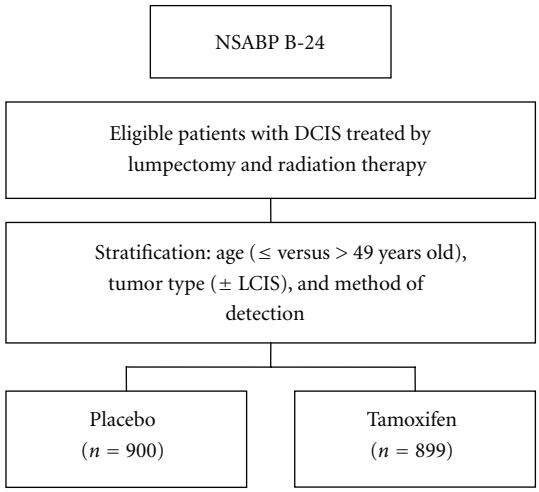


Figure 12: Diagram of NSABP B-24 trial.

As a result of these potential toxicities, as well as the beneficial effect of aromatase inhibitors in the adjuvant treatment of hormone-responsive invasive breast cancer, the NSABP is conducting the B-35 trial designed to compare the effects of tamoxifen and an aromatase inhibitor, anastrozole, on the occurrence of local, regional, distant, or contralateral breast cancer. Postmenopausal women with DCIS, estrogen receptor or progesterone receptor positive, who completed local excision, were randomized to radiation therapy plus 5 years of ongoing treatment with either tamoxifen or anastrozole. The study has completed accrual and may provide additional choices in the treatment of women with DCIS when long-term follow-up results are available.

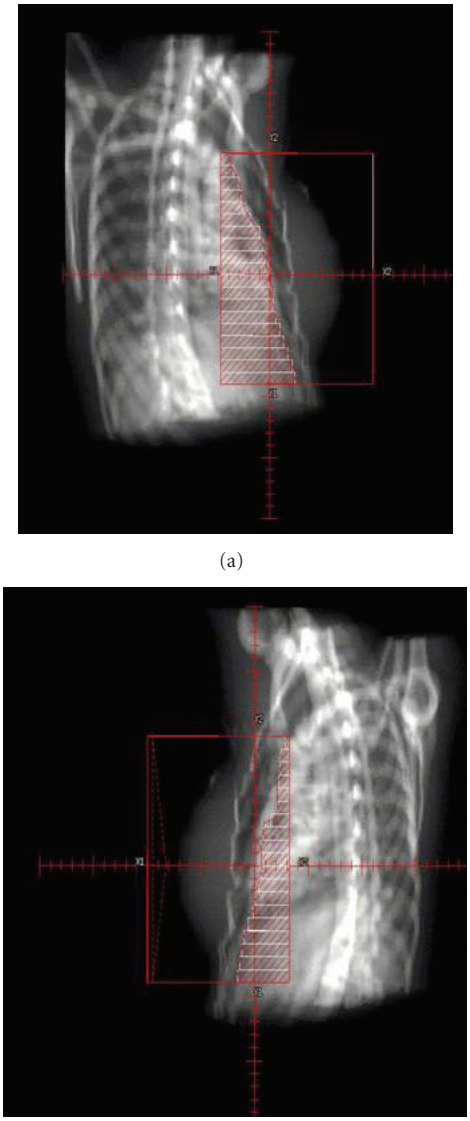
13. Radiation Therapy

Radiation therapy should be delivered after a complete assessment of surgical and pathologic findings, as well as a postoperative mammogram to verify no residual suspicious abnormalities remain. Radiation therapy for DCIS generally consists of treatment to the ipsilateral breast without inclusion of the regional lymph nodes (Figure 13).

The radiation oncologist simulates the treatment field and modern planning is performed with CT-based treatment planning to determine adequate dose homogeneity within the target (Figure 14). CT-based treatment planning also ensures there is minimal dose to the ipsilateral lung and heart.

Standard whole breast radiation is performed through opposed tangential fields on a daily basis, Monday through Friday. Dose is 180–200 cGy per day for a total dose of 4500–5000 cGy, typically delivered over 5–5.5 weeks.

Controversy exists regarding the role of boost irradiation in DCIS. Tumor size, grade, and margin status are often taken into consideration when considering additional dose delivered through a tumor bed boost. In a study of 220 patients with DCIS, 79 patients received a boost, the majority of whom frequently were classified into higher risk categories



(a)

(b)

Figure 13: Standard tangential breast radiation therapy, medial and lateral fields.

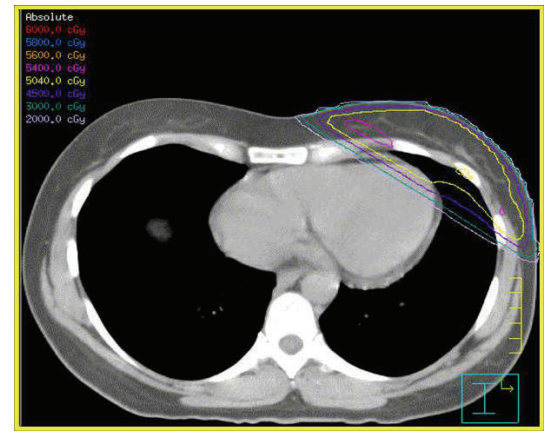


Figure 14: Radiation therapy planning CT with isodose distributions.

as defined by the Van Nuys Prognostic index. Of these 79 patients, none of the patients who received a boost developed a local recurrence compared with 5.7% of patients who did not receive a boost, suggesting a role for radiotherapy boost to the surgical cavity [79].

14. Followup

Patients should have close followup including physical examination every 6 months for at least 5 years to detect recurrent or new primary tumors. Evaluation should include an overall cosmetic result assessment and identification of any acute or chronic sequelae of treatment. Routine tests, such as, bone scan, chest X-ray, CT scan, and liver function tests are not indicated for asymptomatic patients treated for DCIS.

Postsurgical and postradiation changes including skin thickening, edema, and fluid collections will be most marked in the first 6 months. For most patients, radiographic changes will slowly resolve within 2 years of treatment. Mammogram of the treated breast should be performed every 6 months or at more frequent intervals as warranted by clinical or radiographic findings. This schedule should continue until postoperative and postradiotherapy changes have stabilized as judged by a radiologist specializing in breast imaging. Annual mammography of the contralateral breast should continue to be performed according to the guidelines endorsed by both the American College of Radiology and the American Cancer Society.

15. Recurrence

Of the recurrences that occur after primary treatment for DCIS, approximately one-half to two-thirds are cases of invasive cancer [52]. Although no consensus exists, most authors recommend mastectomy for patients with recurrence if breast-conserving therapy was the initial treatment. Systemic therapy is recommended based on standard prognostic factors, such as, nodal and hormonal status to predict the risk for metastasis.

16. Conclusions

DCIS represents a heterogeneous pathologic condition. The incidence of DCIS continues to increase and is most frequently discovered on imaging. Consistent pathologic evaluation is crucial in optimizing treatment recommendations. Surgical treatment options include breast-conserving surgery and mastectomy. Breast-conserving surgery followed by postoperative radiation therapy is considered the standard of care with large randomized trials demonstrating a decrease in the incidence of local recurrence with the addition of radiation therapy. Further study is necessary to determine if a subset of patients with DCIS may require only surgery alone without adjuvant therapy. The optimization of diagnostic imaging, treatment with regards to pathological risk assessment, various irradiation techniques, and the role of endocrine therapy continue to evolve.

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Clinical Study

Is There a Role for Postmastectomy Radiation Therapy in Ductal Carcinoma *In Situ*?

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Background. DCIS treated by mastectomy ensures high local control rates. There is limited data on risk for relapse and lack of clear indication for adjuvant radiation therapy (RT). We report a retrospective review on a population of DCIS patients treated with mastectomy. The objective was to identify the overall incidence of relapse, risk factors for local recurrence, and accordingly for whom adjuvant postmastectomy RT may be considered. *Methods*. This is an IRB-approved retrospective study on a prospective breast cancer database. From 1997 to 2007, we identified 969 patients with diagnoses of DCIS, among them 211 breasts in 207 patients were treated with mastectomy and comprise the study group. *Results*. With a median followup of 55 months (4.6 years) the 10-year relapse-free survival is 97%. Two of 211 breasts (0.9%) treated with mastectomy developed a local-regional recurrence. Both the relapses were among patients defined as having <1 mm final mastectomy margin. *Conclusions*. The rare local relapse after mastectomy limits our ability to reliably identify risk factors for relapse. The consideration for postmastectomy RT should be based on an individualized risk evaluating surgical technique used, presence of BRCA mutation, grade and extent of tumor, and proximity of lesion to the margin of resection.

1. Introduction

With the widespread use of screening mammography, the incidence of DCIS in the USA has exponentially increased over the past 30 years. In 1983, 4800 cases were diagnosed, and in 2011 the incidence had increased to an estimated 57,650 cases [1]. Currently, in the USA approximately one quarter of breast cancers are noninvasive at diagnosis. The surgical treatment for ductal carcinoma *in situ* (DCIS) includes breast conserving surgery (BCS) with or without adjuvant radiation therapy and mastectomy. For an increasing proportion of patients with DCIS, breast conserving therapy is favored. Nevertheless, there are approximately 30% patients in the United States who undergo mastectomy for a variety of reasons that include an inability to obtain clear margins after multiple excisions, the presence of diffuse microcalcifications suspicious for malignancy, BRCA mutation carriers, history of collagen vascular disease, and personal preference [2–5].

Although no prospective randomized trials comparing mastectomy to breast conserving therapy have been completed, the mortality using either treatment is low and the 10-year survival exceeds 95%. Local recurrence following mastectomy is not a common event with estimated recurrence rates in range of 1-2% [5–7]. The aim of this study was to identify the overall incidence of relapse and risk factors for local recurrence, and accordingly for whom adjuvant treatment including postmastectomy radiation therapy may be considered. In addition, this paper includes a review of the literature with a focus on local regional relapse with respect to surgical margins after mastectomy.

2. Methods and Materials

This is an IRB approved retrospective review of a prospectively maintained breast cancer database on patients treated at the Cancer Center at Beth Israel Medical Center and Roosevelt Hospital. Between 1997 and 2010, 969 patients with the

Table 1: Patient characteristics.

Clinical factor	Distribution ($n = 211$)
Age at diagnosis (years)	
(i) <40	20 (9.5%)
(ii) 41–50	86 (40.8%)
(iii) >50	105 (49.7%)
Race	
(i) White	123 (58.3%)
(ii) Black	30 (14.2%)
(iii) Others	58 (27.5%)
Primary method of diagnosis	
(i) Breast Exam	48 (22.7%)
(ii) Mammogram	151 (71.5%)
(iii) Other imaging	12 (5.7 %)
Nuclear grade	
(i) Grade 1	22 (10.4%)
(ii) Grade 2	97 (45.9%)
(iii) Grade 3	92 (43.6%)
Final margins	
(i) Negative	187 (88.6%)
(ii) Close (<1 mm)/Positive	19 (9%)/5 (2.4%)
Receptor status	
(i) ER Positive	42 (19.9%)
(ii) ER Negative	107 (50.7%)
(iii) Unknown	62 (29.4%)

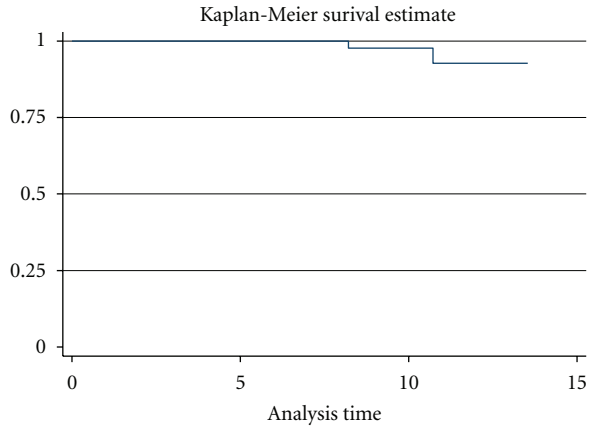

Figure 1: Local-Regional relapse-free survival curve for total cohort ($N = 211$).

diagnosis of DCIS were identified in the database. Among these 207 patients underwent mastectomy. Four patients had synchronous bilateral DCIS treated with bilateral mastectomy. Therefore, 211 breasts (in 207 patients) treated with mastectomy constitute the study group. Patients with new diagnosis of DCIS or concomitant DCIS and lobular carcinoma *in situ* (LCIS) were included. All patients with history of prior invasive and/or microinvasive breast cancer were excluded. All clinical and histopathology characteristics were obtained from the database, cross-referenced with patient charts, and pathology reports were studied. Table 1 summarizes the clinical characteristics. The median age at diagnosis was 50 years (ranging from 25 years to 88 years). In the majority of patients, the cancer was mammographically detected. The surgical procedures included mastectomy alone in 39 (18.5%) cases and mastectomy with sentinel lymph node biopsy or axillary sampling in 172 (81.5%) cases. Nuclear grade 1 was noted in 22 patients, grade 2 in 97 patients, and grade 3 in 92 patients. Resection margins were defined as clinically close and positive when DCIS was noted ≤ 1 mm and was scored as negative in all other instances. Among the study group 88.6% ($n = 187$) had negative margins and 11.4% ($n = 24$) had close or positive margins. None of the patients received postmastectomy radiation therapy (PMRT). Hormonal therapy was variably used at the discretion of the treating oncologist. All patients were followed by the treating physicians at regular intervals.

3. Results

The median followup is 55 months (4.6 years) (Figure 1). The 10-year local regional relapse-free survival is 97%. Among 211 patients, 2 patients developed a local-regional recurrence at 8.2 years and 10.7 years after initial diagnosis. The median time to local regional relapse was 9.5 years. In both instances, the recurrence had an invasive histology, and neither of these 2 patients had a skin sparing mastectomy. Both these failures were among the group of mastectomies reported to have clinical close/positive margins. On further analysis, comparing the 187 patients with negative margins and 24 patients with close/positive margin status, there was a significant correlation with risk for local regional relapse ($P = 0.0125$, Fisher's Exact Test).

The clinical details of the 2 relapses are as follows.

Relapse Case I. The patient was diagnosed with mammographically detected DCIS at age 43. Following initial lumpectomy and reexcision that failed to yield clean margins, the patient underwent total mastectomy with sentinel lymph node biopsy. Final pathology reported intermediate-grade DCIS with associated comedo necrosis. Margin status confirmed DCIS present at the anterior medial-superior margin, and within one millimeter of the anterior margin at the lower inner quadrant, and at the medial-inferior margin. The sentinel lymph node was benign. She received no adjuvant therapies. In a 2007, a follow-up patient who underwent genetic testing was diagnosed to be a BRCA mutation carrier. She was without evidence of disease and underwent prophylactic oopherectomy and contralateral mastectomy at the time. In 2010, at a time interval of 8.2 years from initial diagnosis, she presented with a local recurrence at the superior lateral aspect of the reconstruction. At relapse, the patient underwent wide local excision and axillary lymph node dissection. Pathology confirmed DCIS and invasive recurrence in an area where presumably breast tissue was left behind. In addition, metastases to 7 out of 9 axillary nodes with extracapsular extension were reported. The recurrent tumor was ER and PR positive and Her2 negative.

Table 2: Local recurrence in DCIS following mastectomy—summary of literature.

Author (year)	No. of patients	% LR recurrence	Length of followup in years (median)
Silverstein et al. (1995) [6]	167	2%	10 years
Ciatto et al. (1990) [8]	210	3%	5.5 years (mean)
Cataliotti et al. (1992) [9]	103	3%	10.6 years
Warneke et al. (1995) [10]	75	1.3%	3.6 years
Ringberg et al. (2000) [11]	119	4%	5 years
Carlson et al. (2007) [12]	223	3.1%	6.8 years
Godat et al. (2009) [13]	83	1.1%	4.5 years
Chan et al. (2011) [14]	193	1.7%	8 years
Kelley et al. (2011) [15]	496	3%	6.9 years
Present study	211	0.9%	4.6 years

The patient received systemic chemotherapy, RT, and an aromatase inhibitor. Patient remains free of disease at last followup in January 2012. Remarkablly she also ran the breast cancer marathon in 2011.

Relapse Case II. Mammographically detected DCIS in a 52-year-old female. The patient underwent a total mastectomy with sentinel node sampling. Pathology noted intermediate-grade noncomedo DCIS present 1 millimeter from the superior margin. Three axillary lymph nodes were negative for metastases. Her follow-up history is significant for the diagnosis of an early-stage cervical cancer that was treated surgically. In 2010, at an interval of 10.7 years from initial diagnosis, the patient presented with ipsilateral supraclavicular metastasis. There was no evidence of metastatic disease on the ipsilateral chest wall, and the contralateral breast exam was clinically unremarkable. Pathology confirmed the recurrence to be consistent with breast primary and dissimilar from the cervix. The metastasis was ER and PR positive and Her2 negative. The patient was treated with Arimidex for 18 months and then switched to Faslodex. At the January 2012 followup, the patient remains alive with disease.

4. Discussion

In this retrospective series, very few patients had skin sparing mastectomy and majority of the patients had total mastectomy with lymph node sampling. Currently, however, skin sparing mastectomy is one of the most commonly used techniques. This requires meticulous surgical expertise that preserves skin viability with complete removal of breast parenchyma. The best outcomes are expected with thin skin flaps that reduce the risk for residual breast tissue left behind. The approach of removing pectoralis fascia also minimizes the risk for residual breast tissue and close/positive margins of resection. Studies on patients treated with skin sparing mastectomy yield no increased incidence of local recurrence with this technique compared to conventional mastectomy [12, 17].

The relapses seen after breast conserving therapy in DCIS have a 50-50 chance for being either of *in situ* or invasive histology. However, relapses after mastectomy are mostly invasive as observed in this study and other published reports [13, 16]. The incidence of local-regional relapse rate we observed is similar to other reports in the literature Table 2. Rashtain et al. [16] studied 80 DCIS patients treated by mastectomy and <10 mm surgical margin. With a median followup of 61 months, they reported 7.5% (6/80) rate of local recurrence. Further, it was observed that 5 of these 6 recurrences occurred among the 31 patients with margins $\leq$2 mm compared to 1/6 failures among the 49 patients with greater than 2 mm negative margin. The study by Chan et al. [14] included 193 patients with DCIS treated with mastectomy. They reported a recurrence rate of 1.7%. Among this study cohort, 59 patients were identified to have <5 mm clear margin or positive margin. One of these 59 patients experienced a recurrence. The study by Chan et al. [14] reported an overall recurrence rate of 1.7% among the 59 patients with a <5 mm or positive margin following mastectomy. One of 19 patients (5%) with margin <1 mm had local relapse. On further review by nuclear grade only, they reported 3.3% crude risk of local recurrence among 30 patients who had a high nuclear grade [14]. Godat et al. [13] retrospectively reviewed 87 cases of DCIS treated by mastectomy between 1995 and 2006. The study included patients with microinvasive DCIS and Paget's disease associated with DCIS. With a mean follow-up time of 4.5 years, they observed a relapse rate of 1.1%. Carlson et al. [12] completed a retrospective review of 223 patients who underwent skin sparing mastectomy for DCIS. With a followup of 82.3 months, a relapse rate of 5.1% ($n = 11$) was reported. Among this group, 19 patients were identified with DCIS <1 mm from the surgical margin. Two of the 19 patients presented with local relapse. On univariate analysis, they showed that high tumor grade significantly influenced local relapse but surgical margin status did not reach statistical significance.

One of the 2 local relapses we observed was in a patient who 5 years subsequent to the initial diagnosis and treatment was diagnosed to be a mutation carrier. The retrospective design of the study precluded any systematic evaluation of risk for relapse based on presence of absence of BRCA mutations. Further, both the relapses observed were among the group of 24 patients that had close/positive margins. Although the association of margin status and relapse was statistically significant, we acknowledge that this observation is based on a relatively small sample size with short followup. In the literature, the final margin status is often associated with risk of local relapse [14, 15, 18, 19]. This probably represents an incomplete excision of the initial tumor at the time of mastectomy suggesting undetected residual burden left behind. Alternatively, it could be a new cancer in residual breast tissue. Table 3 is a summary of published literature with a focus on the impact of unfavorable mastectomy margin. The average risk of relapse on the compiled data in Table 3 is 6.4% and is higher than the baseline risk of 0.9–4% observed for all patients (Table 2). Remarkably, the absolute numbers of relapses among patients with close/positive

Table 3: Local-regional relapse following an unfavorable surgical resection margin.

Author	Close margin/positive	No. of patients	No. of relapses	Followup in months
Godat et al. [13]	<5 mm	39	1	54 months
Rashtian et al. [16]	<2 mm	31	5	61 months
Chan et al. [14]	<5 mm	59	1	96 months
Carlson et al. [12]	<1 mm	19	2	82.3 months
Present study	<1 mm	24	2	55 months
Total		172	11 (6.4%)	

margins who are at a higher risk for relapses remain in single digit range. Based on these observations, one may conclude that not all positive/close margins will recur; however, most recurrences observed will have a close/positive margin.

Kelley et al. [15] examined the use of the USC/Van Nuys Prognostic Index (USC/VNPI), a histopathologic scoring system for DCIS patients that takes into account tumor size, nuclear grade, necrosis, margin width, and patient age. They observed that mastectomy patients with a high USC/VNPI score may be at increased risk for local recurrence reporting overall local relapse rate of 3% at a mean follow-up time of 83 months. The probability of recurrence among patients scored between 10–12 was 9.6% compared to 0% for those scoring 4–9 at 12 years. The authors suggested that utilization of a clear margin on segmental excision serves as a surrogate for extensive DCIS. In this series, the average tumor extent of the 11 patients experiencing recurrence is 5.6 cm and all had multifocal disease. Although the authors report a correlation between their calculated USC/VNPI scores and recurrence, it is worth noting that the margin data used in the scores referred to premastectomy margins, that is, margins that were obtained after excision or biopsy but before mastectomy. The investigators might have arrived at different conclusions had the USC/Van Nuys Prognostic Index used the final mastectomy margins. More likely it is the final margin status of the mastectomy sample that would impact local recurrence [15].

Salvage after relapse has been reported by Kim et al. [18] This study reported on the largest number of postmastectomy recurrences to date and included a review of 10 chest wall relapses. Among these 10 patients, the common risk factors included young age, as well as multiquadrant DCIS, suggesting probability of residual breast tissue left behind after mastectomy. The patients in this study had their primary cancers treated at different institutions; therefore, this study cited a number of limitations, including lack of a comparison group, absence of data on mastectomy margins, and differences in standards of treatment among different institutions. Among the 10 recurrences observed, 9 were successfully salvaged with excision and radiation therapy at the time of relapse. The high salvage rate with surgery and radiation therapy suggests that delayed approach to PMRT for patients thought to have higher than baseline risk may be reasonable. With this approach, the routine application of PMRT with its attended late side effects can be avoided.

In summary, the risk of relapse is low and there is evidence that salvage therapy including surgery and RT is highly effective [20, 21]. The rare local relapse after mastectomy limits our ability to acquire substantial evidence on the risk factors for relapse in DCIS. The low statistical power, to some extent, explains the lack of a clear consensus on this subject. Postmastectomy studies on DCIS that have tried to evaluate the impact of margin status have drawn conclusions based on very small numbers and through retrospective studies with inherent biases. Therefore, in clinical practice, the application of PMRT remains limited to an individualized risk determined at the discretion of the treating physicians. Such individualized assessment should include surgical technique used, extent of margin involvement, DCIS grade, and extent of tumor. Future research exploring the risk of relapse based on presence or absence of BRCA mutations and potential contribution of molecular breast cancer biomarkers including Oncotype Dx, HOXB-13, and others yet to be defined may guide the individual risk categorization for local relapse and accordingly the role for adjuvant therapies.

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Review Article

Memorial Sloan-Kettering Cancer Center: Two Decades of Experience with Ductal Carcinoma In Situ of the Breast

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Researchers at Memorial Sloan-Kettering Cancer Center have investigated many aspects of their experience with ductal carcinoma in situ of the breast over the past 20 years. This paper summarizes the most clinically relevant findings.

1. Introduction

Since its founding in 1884 as the New York Cancer Hospital, Memorial Sloan-Kettering Cancer Center (MSKCC) in New York, NY, has concentrated its clinical and research efforts on the diagnosis and management of cancer. This review summarizes MSKCC's work on ductal carcinoma in situ (DCIS) of the breast.

2. Mammographic Features of DCIS and Its Recurrences

In the late 1980s and early 1990s, increasing screening mammography resulted in increasing detection of clinically occult carcinomas, including DCIS. From 1973 to 1992, the incidence of DCIS increased by 557%, from 2.4 to 15.8 per 100,000 women [1]. Prior to widespread screening mammography, DCIS constituted 0.8% to 5.0% of all breast carcinomas; by 1996 it constituted 14% [2, 3].

In these early days, when the diagnosis of DCIS was exponentially increasing, Dershaw et al. attempted to define the mammographic features of DCIS. They retrospectively reviewed mammograms, specimen radiographs, and pathology reports for 51 patients with DCIS treated in the 1980s [4]. DCIS was radiographically evident as microcalcifications alone in 68% and as microcalcifications within a mass in 30%. Several radiographic findings indicated multifocal disease: mass larger than 2.5 cm; more than one mass; more than one cluster of microcalcifications; or parallel linear intraductal calcifications. This work demonstrated that in the overwhelming majority of patients, DCIS presents as mammographically evident microcalcifications and that specific mammographic findings may suggest multifocal disease.

During the 1980s and 1990s, breast surgery for DCIS became progressively less invasive. No randomized trial was ever performed comparing breast conservation to mastectomy for DCIS. However, as results from Fisher et al. [5] and Veronesi et al. [6], which proved that breast-conserving surgery (BCS) plus radiation was equivalent to total mastectomy (TM) for invasive cancer, were assimilated, it was assumed that the same findings would hold for DCIS. In 1983, 71% of patients with DCIS were treated with TM, and by 1992, only 44% were [1].

TM eliminates the need for postoperative screening mammography; BCS does not—the remaining breast requires continued surveillance for ipsilateral breast tumor recurrences (IBTRs). This was the focus of investigation of Liberman et al. [7]. They performed a retrospective review of 162 patients treated with BCS for DCIS between 1978 and 1990. Median follow-up was 75 months (range, 3–210 months). Thirty-three (20%) were diagnosed with IBTRs; of these, mammograms were available for review in 20. Median time to IBTR was 26 months (range, 6–168 months);

IBTRs were DCIS-only in 13 (65%), and in-situ and invasive ductal carcinoma in 7 (35%). They found that: (1) 95% of IBTRs were mammographically evident (85% detectable only mammographically; 10% detectable mammographically and by palpation; 5% detectable only by palpation); (2) IBTRs were mammographically evident whether they were DCIS or invasive; and (3) 90% of IBTRs demonstrated calcifications, of which 79% demonstrated a mammographic pattern identical to the primary tumor (clustered versus linear versus multiple versus regional versus segmental), and of which 82% demonstrated a mammographic morphology identical to the primary tumor (linear versus pleomorphic versus punctate). Liberman et al. definitively demonstrated that mammography can detect IBTRs in patients who undergo BCS for DCIS.

3. Sentinel Lymph Node Metastasis in Patients with DCIS: Incidence and Clinical Implications

Cody et al. [8] and Cody and Van Zee [9] ask: "Is axillary node staging required in patients with DCIS of the breast?" Its nomenclature would suggest that DCIS is incapable of breaking through the ductal basement membrane, of accessing breast parenchyma or lymphatic channels, and of spreading locally, regionally, or distantly. In fact, Lagios and Silverstein argue that sentinel lymph node biopsy (SLNB) is "dangerous and unwarranted" in the setting of DCIS [10]. They are correct: searching for metastatic spread of a lesion that is by definition incapable of metastatic spread may yield potential problems—one may find nothing, thereby wasting effort, time, and health care resources, or one may induce harm by causing morbidity, including the most feared complication of axillary surgery: lymphedema [11, 12]. In a sense, Cody and Van Zee agree with Lagios and Silverstein. They argue that "the strongest argument for sentinel lymph node (SLN) biopsy in DCIS is the diagnostic uncertainty and inherent sampling error of conventional pathologic techniques. SLN biopsy is indicated in any DCIS patient who may have an underlying invasive cancer, especially those who require mastectomy" [9]. Two studies from MSKCC attempt to evaluate these arguments.

Klauber-DeMore et al. performed a clinical audit of 76 patients with DCIS and 38 patients with DCIS with microinvasion (DCIS-MI), all of whom underwent SLNB between 1997 and 1999 [13]. "Patients with DCIS were considered to be at high risk and were selected for SLN biopsy if there was sufficient concern that an invasive component would be identified in the specimen during the definitive surgery." These high-risk patients had a palpable mass (21%), mammographic mass (34%), histology suspicious but not diagnostic for microinvasion (24%), multicentric disease requiring TM (53%), or high nuclear grade or non-high nuclear grade with necrosis (72%). DCIS-MI was in and of itself high-risk.

For patients with DCIS, 9 (12%) had a positive SLN. Seven of these patients had isolated tumor cells positive only by immunohistochemistry—what is currently categorized as pN0(i+) according to the subsequently revised American Joint Commission on Cancer (AJCC) staging system, 6th Edition (2002) and 7th Edition (2010). Upon completion axillary lymph node dissection, 1 patient had additional macrometastasis (>2 mm) positive by routine hematoxylin and eosin (H&E). These findings prompted re-evaluation of primary-tumor specimens. One patient had a focus of microinvasion, one patient had a metastatic invasive carcinoma of the contralateral breast, and 2 patients had lymphovascular invasion despite no evidence of stromal invasion.

For patients with DCIS-MI, 3 (10%) had a positive SLN: one macrometastasis positive by routine H&E; one micrometastasis positive by routine H&E and immunohistochemistry; and one with isolated tumor cells positive by immunohistochemistry. Upon completion axillary lymph node dissection, no further positive nodes were found. Re-evaluation of primary-tumor specimens revealed invasion greater than 1 mm in 2 patients, changing the tumor status from T*is* to T1mi. Furthermore, one of these patients demonstrated in-breast lymphatic invasion.

Klauber-DeMore et al. demonstrated that the frequencies of positive axillary SLNs, including isolated tumor cells in patients with DCIS in whom the surgeon was concerned that invasion was present and in patients with DCIS-MI, were 12% and 10%, respectively [13]. Moore et al. sought to evaluate the clinical relevance of such involvement [14]. Between 1994 and 2002, 2159 patients underwent surgery for DCIS at MSKCC, the John Wayne Cancer Institute, or the University of Southern California. Of these, 470 patients underwent SLNB. As in the previous report, for the most part, these patients had high-risk DCIS.

Forty-three (9%) had a positive SLN. Of these, 3 (7%) had macrometastases, 4 (9%) had micrometastases, and 36 (84%) had isolated tumor cells. Re-evaluation of primary-tumor specimens demonstrated that 2 (5%) had DCIS-MI and 2 (5%) had lymphovascular invasion. Ultimately, 9 of 43 (21%) high-risk DCIS patients with a positive SLN, and 9 of 470 (2%) of all high-risk DCIS patients were upstaged to stage 1 or stage 2 (AJCC 6th Edition) as a direct result of SLNB. Based on these findings, 16 patients (37%) received chemotherapy. At median follow-up of 27 months (range, 3–88 months), one patient with isolated tumor cells in her SLN developed hepatic metastases and died of disease. Re-evaluation of her primary-tumor specimen demonstrated previously unidentified microinvasion. Finally, Moore et al. found 2 factors associated with SLN positivity for patients with DCIS: extensive disease requiring mastectomy (12% versus 4%, $P = 0.016$) and presence of necrosis (11% versus 3%, $P = 0.04$).

In summary, these 2 reports conclude that approximately 1 of 10 patients with high-risk DCIS or DCIS-MI have evidence of axillary metastases on SLNB, including macro- or micrometastases, and isolated tumor cells. And of these, only about 20% are considered upstaged according to the AJCC 6th Edition staging system (and 26% according to the AJCC 7th Edition staging system). Therefore, only about 2% of all women with high-risk DCIS or DCIS-MI are upstaged due to SLN findings. In conclusion, while SLNB should not be routinely used for DCIS, it is appropriate in women

undergoing TM or in women in whom the suspicion of invasive carcinoma is high.

4. Utility of Preoperative MRI for Paget's Disease of the Breast

Paget's disease of the breast usually presents with eczematous changes of the nipple-areola complex, such as erythema, scaling, and itching [15]. In-situ or invasive carcinoma usually underlies these epidermal changes [16]. Thus, upon clinical or pathologic diagnosis, breast imaging is pursued in an effort to characterize the extent of the underlying associated cancer. Mammography has been the mainstay of radiologic work-up. Morrogh et al. sought to evaluate the utility of MRI as a complementary imaging modality [17].

The authors retrospectively reviewed the charts of 34 patients who presented between 1995 and 2005 with changes in the nipple-areola complex consistent with Paget's disease [17]. Patients with a prior history of ipsilateral breast carcinoma were excluded. All 34 patients underwent preoperative mammography; 13 underwent preoperative MRI. All underwent surgery, and, on final pathology, 32 of 34 patients (94%) had an underlying cancer (DCIS, 56%; DCIS-MI, 18%; invasion, 21%) and 2 of 34 patients (6%) had an underlying benign lesion (atypical ductal hyperplasia, 3%; or intraductal papilloma, 3%).

Preoperative mammography identified 11 of 32 (34%) cancers, accurately demonstrating extent of disease in 9. Among the 13 women who underwent MRI, MRI identified 7 of 12 (58%) cancers, accurately demonstrating extent of disease in 6. After a positive mammogram, subsequent MRI did not alter course of treatment. However, after a negative mammogram, subsequent MRI detected otherwise-occult disease in 4 of 8 patients, accurately demonstrating extent of disease in all. Overall, mammography had 100% positive predictive value, 9% negative predictive value, 34% sensitivity, and 100% specificity, while MRI had 100% positive predictive value, 17% negative predictive value, 58% sensitivity, and 100% specificity.

In this series, there was no benefit of MRI in patients with positive mammography. However, in patients with negative mammography, MRI demonstrated an underlying occult cancer and the extent of that cancer in about half, thus providing a diagnosis and facilitating surgical treatment. The ability to determine extent of disease was tantamount, for it enabled the surgeon to determine the feasibility of BCS. In this study, 59% of patients had disease confined to the central part of the breast. Thus for patients with Paget's disease of the breast and a negative mammogram, MRI is helpful in detecting the presence and extent of occult, underlying carcinomas.

5. Age: Associations with Local Recurrence of DCIS and with DCIS Treatment Practice Patterns

Early after the publication of randomized studies proving the equivalency of BCS with adjuvant radiotherapy and TM for invasive carcinoma, clinicians and patients slowly adopted BCS for DCIS. Van Zee et al. investigated MSKCC's early experience with BCS for DCIS [18]. They performed a retrospective analysis of 157 patients with DCIS treated with BCS between 1978 and 1990 with a median follow-up of 74 months. Of 157 patients, 33 (21%) were diagnosed with IBTRs. The actuarial IBTR rate was 16.1% at 6 years. Among those who received radiotherapy, the 6-year IBTR rate was 9.6%; without radiotherapy, it was 20.7% ($P = 0.05$). On univariate analysis, clinicopathologic features associated with lower IBTR rates were older age, noncomedo subtype, lower nuclear grade, negative margins, and adjuvant radiotherapy. For patients less than 40 years old, the 6-year IBTR rate was 47.2%; for patients 40–69 years old, the 6-year IBTR rate was 14.0%; for patients 70 years old or greater, the 6-year IBTR rate was 10.8%. Compared to younger patients, lower IBTR rates were seen in older patients whether adjuvant radiotherapy was used or not. IBTR rates with and without radiotherapy for the 3 age groups were <40 years old: 33.3% and 59.2%; 40–69 years old: 8.5% and 19.1%; ≥70 years old: 0.0% and 14.4%, respectively. Compared to younger patients, older patients tended to have lower nuclear grades and were less likely to receive adjuvant radiotherapy, but no factor (including clinical presentation, tumor size, comedo subtype, nuclear grade, presence of necrosis, margin status, or adjuvant radiotherapy) demonstrated a statistically significant association with age. This study showed that compared to older patients, younger patients treated with BCS for DCIS are more likely to develop IBTRs and that they are at a relatively high risk for IBTRs.

This finding, which had not been previously shown for DCIS, has also been observed by Veronesi et al. for invasive carcinoma. He found that women who underwent quadrantectomy alone for invasive carcinomas had an IBTR rate of 17.5% if they were 45 years of age or younger, and 3.8% if they were 55 years of age or older [19]. Veronesi et al. surmised that with age, "the complex structure of the mammary gland disappears and the breast is reduced to a fatty organ with scattered islands of fibroepithelial tissue, without connections between them."

BCS attempts to balance oncologic and cosmetic imperatives—to treat cancer while maintaining the size and shape of the native breast. Ideally, a surgeon excises a primary tumor to clear margins and leaves as much normal tissue intact as possible. In a sense, TM allows for the biggest possible margin and, in doing so, achieves oncologic imperatives, but pays the cosmetic price of complete removal of the breast. Conversely, a limited tumorectomy allows for the smallest possible margin and, in doing so, achieves cosmetic imperatives, but is associated with higher rates of IBTR. This may have been particularly true prior to the 1980s, when diligent microscopic assessment of inked margins was not standard.

Hwang et al. postulated that volume of surgical resection may be related to age, which at least partially explains the observation that older women have lower IBTR rates compared to younger women [18, 20]. Older women tend to have higher BMIs and larger breasts, perhaps allowing surgeons to do wider resections. Furthermore, it may be

possible that the oncologic-cosmetic balance of BCS is tipped toward wider margins and away from cosmesis in older patients compared to younger patients.

Hwang et al. hypothesized that surgeons were more willing to take larger volumes of tissue in older patients compared to younger patients, increasing IBTR-free survival but possibly compromising cosmesis. They retrospectively reviewed the same population studied by Van Zee et al. and found 126 cases with available information regarding the volume of resection. They found that while tumor size, margin status, histologic subtype, nuclear grade, and size did not correlate with volume of resection, patient age did—younger patients had significantly smaller volumes of resection than older patients ($P = 0.03$). Patients with smaller volumes of resection had higher 6-year IBTR rates than patients with larger volumes of resection (21% versus 5.6%; $P = 0.16$). Also, patients with smaller volumes of resection were more likely to undergo adjuvant radiotherapy than patients with larger volumes of resection, though both groups benefited. For the small volume-of-resection group, the IBTR rate was 12.7% with adjuvant radiotherapy and 29.1% without adjuvant radiotherapy. For the large volume-of-resection group, the IBTR rate was 0% with adjuvant radiotherapy and 7.1% without adjuvant radiotherapy.

In summary, Hwang et al. conclude that older patients tend to have larger volumes of resection, which is associated with lower rates of IBTR, even in the absence of adjuvant radiotherapy. There are 3 possible reasons for this. First, "smaller resection volumes may be used in younger patients to achieve a better cosmetic result, possibly contributing to a high local recurrence" [20], showing that the oncologic-cosmetic balance is tipped away from oncologic imperatives toward cosmetic ones. This had been suggested by the Joint Center for Radiation Therapy for women with invasive breast cancer [21]. Second, as stated previously, in older patients, "the complex structure of the mammary gland disappears and the breast is reduced to a fatty organ with scattered islands of fibroepithelial tissue, without connections between them" [19]; the older breast is anatomically and physiologically less likely to have a diffuse distribution of DCIS and therefore less prone to have unresected microscopic disease. Third, the biology of breast cancer in younger patients is intrinsically more aggressive than the biology of breast cancer in older patients; compared to younger patients, older patients tend to have low nuclear grades and hormone-receptor positivity [20, 22, 23].

Ho et al. expand upon the aforementioned works by Van Zee et al. and Hwang et al. [18, 20] and "aimed to determine the impact of increasing age and other clinicopathologic features on treatment patterns and outcomes in older women with DCIS" [24]. The analysis of Van Zee et al. included 157 patients (of any age) treated with BCS for DCIS over a 12-year period. The analysis of Ho et al. included 646 patients (60 years of age or older) treated between 2000 and 2007 (2 decades after those studied by Van Zee et al. and Hwang et al.), of whom over 75% underwent BCS. Though reasons for this increase are certainly multiple, it is clear that over the past 20 years, widespread screening mammography has resulted in more frequent detection of DCIS and that more and more patients are being treated with BCS than with TM. Ho et al. included 646 patients, despite restricting their study population to those 60 years old or older. This supports the notion that the United States population at large, and cancer patients in particular, are aging. In 2010, 25,000 women 65 years of age or older were diagnosed with DCIS; it is estimated that, in 2030, 39,000 women 65 years old or older will be diagnosed with DCIS, a 56% increase [25].

Ho et al. found that even among older patients, the oldest received less aggressive therapy—for patients aged 60–69 years, 45% received TM, 25% received BCS with radiotherapy, and 30% received BCS alone; for patients aged 70–79 years, 38% received TM, 20% received BCS with radiotherapy, and 40% received BCS alone; for patients aged 80 years or more, 16% received TM, 13% received BCS with radiotherapy, and 71% received BCS alone ($P < 0.001$). In addition to younger age ($P < 0.001$), higher grade ($P < 0.001$) and the presence of necrosis ($P < 0.01$) were associated with TM or radiotherapy.

Median follow-up was 54 months (range, 6–112 months). The 4-year local recurrence rate was 3.6% and differed according to treatment. None of the TM group, 4% of the BCS-radiotherapy group, and 5% of the BCS-alone group experienced a local recurrence at 4 years ($P < 0.005$). When the BCS-radiotherapy and BCS-alone groups were compared, no statistically significant differences in local recurrence were detected ($P = 0.66$). Besides treatment, no other factors—including age—were associated with local recurrence.

The study of Ho et al. is neither randomized nor controlled. Rather, it is a clinical audit; its data are the end-results of innumerable individualized medical decisions. Most patients with BCS did not receive radiotherapy in spite of data from 4 randomized controlled trials that definitively show a lower IBTR rate among those that receive adjuvant radiotherapy [26–29]. Nonetheless, the omission of adjuvant radiotherapy did not translate into substantially different IBTR rates, at least in this patient population. That older women were less likely to experience an IBTR—despite not undergoing adjuvant radiotherapy—suggests that clinicians are able to individualize treatment appropriately. These findings also demonstrate that, in the current era, older women have lower rates of IBTR, confirming the findings of Van Zee et al. and Hwang et al. [18, 20].

6. Association of Lobular Neoplasia with Local Recurrence of DCIS

Rudloff et al. sought to determine whether the associated histologic findings of columnar cell changes, atypical ductal hyperplasia, or lobular neoplasia affected IBTR rates in patients who underwent BCS for DCIS [30]. They state that "the presence of concurrent proliferative lesions associated with in situ or infiltrating breast carcinoma may reflect underlying gene perturbations of cancer-related pathways in the uninvolved ductal epithelium, which could be markers of disease risk, occult disease, or, also, the tissue response to an existing tumor." This study included 294 patients

with DCIS treated with wide local excision, with or without radiotherapy, between 1991 and 1995, and included re-review of all available pathology slides. Median follow-up was 11 years (range, 0–16 years). Columnar cell changes were present in 71 (24%), atypical ductal hyperplasia in 37 (13%), and lobular neoplasia in 41 (14%). Fifteen of 41 patients (37%) with lobular neoplasia developed an IBTR; 40 of 227 patients (18%) without lobular neoplasia developed an IBTR (hazard ratio, 2.49; $P = 0.001$). On multivariate analysis, 5-year, 10-year, and 15-year IBTR rates were twice as high in women with DCIS and associated lobular neoplasia (26%, 36%, and 55%, respectively) compared to women with DCIS alone (14%, 19%, and 24%, respectively) ($P = 0.002$). In fact, the presence of lobular neoplasia and the omission of adjuvant radiotherapy demonstrated similar increases in IBTR rates. Columnar cell changes and atypical ductal hyperplasia did not demonstrate increased IBTR rates ($P = 0.44$ and $P = 0.20$, respectively). This paper found that the presence of lobular neoplasia is associated with increased IBTR rates in patients undergoing BCS for DCIS.

The authors hypothesized that "concurrent lobular neoplasia may be a phenotypic manifestation of more extensive genetic abnormalities, resulting in a higher risk for local recurrence." They called for assessment of the surrounding epithelium to further evaluate these findings in future clinical studies of BCS for DCIS. Furthermore, the authors suggested that if patients with DCIS and concurrent lobular neoplasia are at higher risk, they may particularly benefit from the use of risk-reducing adjuvant therapies.

7. Association of Margin Width and Volume of Disease Near Margin with Local Recurrence of DCIS

Silverstein et al. found that the IBTR rate was 3% at 8 years for women who had margins at least 1 cm in width and therefore proposed that radiotherapy could be omitted in women with DCIS who undergo BCS and have very wide margins [31, 32]. To test this hypothesis, Rudloff et al. further examined their previous exhaustively characterized population of 294 patients [33]. They had a median follow-up of 11 years. They categorized patients into the same groups used by Silverstein et al.: close or positive (margin width <1 mm), intermediate (margin width =1–9 mm), and widely clear (margin width ≥10 mm). Furthermore, Rudloff et al. quantified the number of ducts involved with DCIS at this margin width as 1 or ≥2. They combined these 2 characteristics into a measure of volume of disease near the margin, such that each patient was categorized as: (1) widely clear margin ≥10 mm, 0 involved ducts within 10 mm of margin; (2) margin width 1 to 9 mm, 1 involved duct at the closest margin; (3) margin width <1 mm, 1 involved duct at the closest margin; and (4) margin width <10 mm, ≥2 involved ducts at the closest margin.

Rudloff et al. found that women with DCIS presumed to be at higher risk of IBTR, including those with higher nuclear grade or necrosis, were more likely to receive radiation than those presumed to be at lower risk ($P < 0.009$). Nonetheless, women receiving radiotherapy had lower rates of IBTR (10-year rates without radiotherapy, 28% versus with radiotherapy, 12%; $P = 0.002$), which is consistent with randomized controlled trials [26, 34]. While adjuvant radiotherapy benefited all populations, it benefited those with closer margins more than those with wider margins. Adjuvant radiotherapy "reduced adjusted IBTR rates by 62% ($P = 0.002$) for all patients; by 83% for lesions with <1 mm margins ($P = 0.002$), by 70% for 1 to 9 mm ($P = 0.05$), and by 24% ($P = 0.55$) for ≥10 mm." In other words, among patients who did not receive radiotherapy, margin status was significantly associated with IBTR ($P = 0.02$), but receipt of radiotherapy negated any influence of margin width on the risk of IBTR ($P = 0.66$). Because in this series, radiotherapy was given according to clinical judgment in a non-randomized fashion, Rudloff et al. went on to perform a multivariate analysis to adjust for the many other factors that could influence the association between margin width and added value of radiotherapy in reducing IBTR rates (age, palpable mass, lobular neoplasia, nuclear grade, necrosis, endocrine therapy, and number of involved ducts at closest margin). It was unchanged.

Rudloff et al. then proceeded to analyze the association of volume of disease near margin, incorporating margin width and number of involved ducts at the closest margin with IBTR. Among those not receiving radiotherapy, they found that the higher the volume of disease near the margin, the greater the risk of IBTR, with a hazard ratio of 3.37 ($P = 0.002$) for IBTR among patients who had ≥2 involved ducts and <10 mm margin width. However, among those receiving radiotherapy, there was no increased risk of IBTR. Stratified by volume of disease near margin, they showed that the risk reduction associated with radiotherapy was the greatest in those with the highest volume of disease near the margin (hazard ratio of radiotherapy to no-radiotherapy, 0.14; $P = 0.004$) as compared to those with widely clear margins (0 involved ducts within 10 mm of margin; hazard ratio of radiotherapy to no-radiotherapy, 0.60; $P = 0.39$).

Like others [35, 36], Rudloff et al. were unable to identify a subgroup with a very low rate of IBTR without radiotherapy; the 10-year IBTR rate for their most favorable subgroup (patients with wide margins and older age, and without a palpable mass or lobular neoplasia) was 13%. Interestingly, this rate is comparable to the IBTR rate observed in the population that did receive radiotherapy in the Rudloff study (12%) and among the populations that received radiotherapy in randomized controlled trials (9–20% at 8–17 years) [28, 34, 37, 38]. These findings support the concept that the added benefit of radiotherapy varies among DCIS patients of different risk; in other words, the benefit-to-risk ratio is not the same for all DCIS patients. For women with a higher volume of disease near the margin, radiotherapy is associated with a greater risk reduction of IBTR.

8. Integrating Clinical and Treatment Factors to Estimate Risk of Local Recurrence of DCIS

For patients undergoing BCS for DCIS, randomized controlled trials demonstrate that adjuvant radiotherapy and

hormonal therapy reduce IBTR rates by 50% and 30%, respectively [26, 34, 38]. However, because these treatments are not without risk and because there is no observed survival benefit associated with either, expert clinicians do not support their ubiquitous utilization [39, 40]. Some populations may be at sufficiently low risk of IBTR such that the benefit-to-risk ratio of adjuvant treatment is not justified. Rudloff et al. argue that "the one-size-fits-all approach of adjuvant treatment for all patients with DCIS seems counterintuitive to both the molecular heterogeneity of DCIS as well as the increasing trend toward individualized cancer treatment" [41]. The work of Rudloff et al. discussed above certainly supports the idea that the benefit-to-risk ratio of adjuvant treatment varies with the risk of IBTR for a woman with DCIS. In their next investigation, Rudloff et al. aimed to provide clinicians with the means of providing that "individualized cancer treatment." Several clinicopathologic factors have been shown to affect IBTRs in patients undergoing BCS for DCIS. These include age, clinical presentation, family history, tumor size, tumor multifocality, margin status, volume of disease at the closest margin, histologic architecture, nuclear grade, and necrosis. Rudloff et al. combine these, as well as treatment factors, to create a clinically useful tool, a nomogram, that integrates the information available in all of these factors in order to estimate risk of IBTR for women undergoing BCS for DCIS. To build this nomogram, Rudloff et al. evaluated 1681 patients treated with BCS for DCIS between 1991 and 2006. Median follow-up was 5.6 years (range, 0–17.5 years). Actuarial 5-year and 10-year IBTR rates were 9% (95% confidence interval (CI) 8–11%) and 15% (95% CI, 13–18%), respectively.

The nomogram includes 10 parameters (age at diagnosis, family history, initial presentation, radiotherapy, endocrine therapy, nuclear grade, necrosis, margins, number of excisions, and year of surgery), which are assigned a score between 0 and 100. The sum of these 10 individual scores is used to determine the 5- and 10-year risk of IBTR. Rudloff et al. provide examples: "The nomogram predicts that a 70-year-old woman (30 points) without family history of breast cancer (0 points), with screen-detected (0 points) DCIS with low nuclear grade (0 points), no necrosis (0 points), and negative margins (0 points) after one re-excision (0 points) who does not undergo RT (100 points) or anti-estrogen therapy (76 points) has a lower than 10% risk (total points: 206) of developing a recurrence within 10 years of BCS. Conversely, a 40-year-old woman (75 points) with a family history of breast cancer (30 points) and DCIS detected as a palpable mass (34 points), who underwent one excision (0 points) resulting in close margins (56 points), with high nuclear grade (27 points) and necrosis (13 points), and who defers RT (100 points) and endocrine therapy (76 points), has about a 50% risk (total points: 411) of developing an IBTR by 10 years."

The nomogram was internally validated with bootstrapping, and was recently validated in independent populations by Collins et al. [42] and Yi et al. [43]. The nomogram utilizes the many discrete factors that have been shown to affect risk of IBTR and combines them into a user-friendly calculator to estimate risk. Using these readily available factors, this tool can assist clinicians in weighing the pros and cons of various surgical options and adjuvant therapies for DCIS.

9. Summary

This paper summarizes the investigations of DCIS by the Breast Surgical Service at MSKCC over the past 2 decades. It includes papers investigating the mammographic features of DCIS and its recurrences, the incidence and clinical implications of SLN metastases in patients with high-risk DCIS, the utility of preoperative MRI for Paget's disease of the breast, the associations of age with local recurrence and practice patterns for treatment of DCIS, the association of concurrent lobular neoplasia with local recurrence of DCIS, the association of margin width and volume of disease near margin with local recurrence of DCIS, and the creation of a nomogram that incorporates many factors simultaneously to estimate risk of IBTR of DCIS.

Abbreviations

AJCC:	American Joint Commission on Cancer
BCS:	Breast-conserving surgery
CI:	Confidence interval
DCIS:	Ductal carcinoma in situ
DCIS-MI:	Ductal carcinoma in situ with microinvasion
H&E:	Hematoxylin and eosin
IBTR:	Ipsilateral breast tumor recurrence
MSKCC:	Memorial Sloan-Kettering Cancer Center
SLN:	Sentinel lymph node
SLNB:	Sentinel lymph node biopsy
TM:	Total mastectomy.

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Review Article

Ductal Carcinoma *In Situ*: Recent Advances and Future Prospects

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Introduction. This article reviews current management strategies for DCIS in the context of recent randomised trials, including the role of sentinel lymph node biopsy (SLNB), adjuvant radiotherapy (RT) and endocrine treatment. *Methods.* Literature review facilitated by Medline, PubMed, Embase and Cochrane databases. *Results.* DCIS should be managed in the context of a multidisciplinary team. Local control depends upon clear surgical margins (at least 2 mm is generally acceptable). SLNB is not routine, but can be considered in patients undergoing mastectomy (Mx) with risk factors for occult invasion. RT following BCS significantly reduces local recurrence (LR), particularly in those at high-risk. There remains a lack of level-1 evidence supporting omission of adjuvant RT in selected low-risk cases. Large, multi-centric or recurrent lesions should be treated by Mx and immediate reconstruction should be discussed. Adjuvant hormonal treatment may reduce the risk of LR in selected cases with hormone sensitive disease. *Conclusion.* Further research is required to determine the role of new RT regimes and endocrine therapies. Biological profiling and molecular analysis represent an opportunity to improve our understanding of tumour biology in DCIS to rationalise treatment. Reliable identification of low-risk lesions could allow treatment to be less radical.

1. Introduction

1.1. Diagnosis. The introduction of national mammographic screening programmes and the increasing use of digital mammography and MRI have dramatically changed the clinical presentation of DCIS. Prior to this, DCIS made up a small proportion of all breast malignancy and was only diagnosed in patients presenting with a palpable mass, pathological nipple discharge, or occasionally found as an incidental biopsy finding [1, 2]. In contrast, it is now most frequently identified in asymptomatic women with screen-detected micro calcifications [3] and makes up a larger proportion of breast malignancy. Approximately one fifth of all screen-detected breast cancers are now DCIS [4].

Although the rates of all breast malignancy have increased with time, between 1980 and 1995, Western countries have experienced a four-fold "increase" in the incidence of DCIS specifically, particularly in women of screening age [5].

Data from a systematic review of 374 studies reported the pooled incidence of DCIS in the early 1970s as 5.8/100000 and this had risen to 32.5/100000 in 2004 [6]. A higher proportion of the cases post screening were non comedo DCIS, which is considered less aggressive.

Screening and cancer registry data from Norway including 2.3 million women reported in 2010 showed an increase in incidence of DCIS from 4/100000 before the introduction of screening to 11/100000 postintroduction. In women of screening age, the proportion of DCIS within breast malignancy rose from 5% to 13%. Age-standardised rates of all breast cancer including DCIS increased over time in those of screening age, but a large peak at the point screening was introduced, subsequent drop in incidence (but not to pre-screening levels), then a steady climb over time. Rates were also higher in prevalent as opposed to incident screens [7].

These studies seem to suggest that the introduction of screening is largely responsible for the apparent increased incidence of DCIS in recent times, but that the stage of the disease may be much earlier and possibly less clinically relevant [6].

The trend is likely to continue with further technological advances, including the transition from analogue to full-field digital mammography (FFDM) and the development of computer-aided detection (CAD) [8].

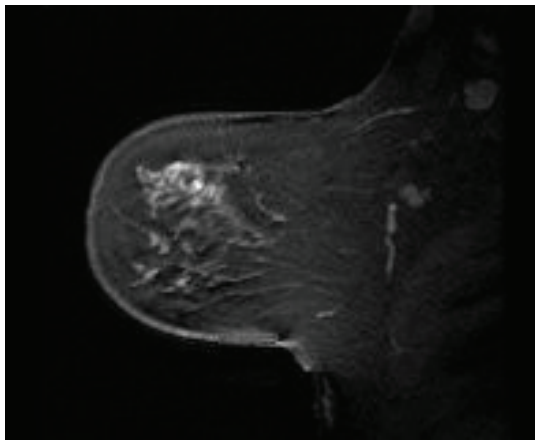

Figure 1: MRI appearance of recurrent DCIS.

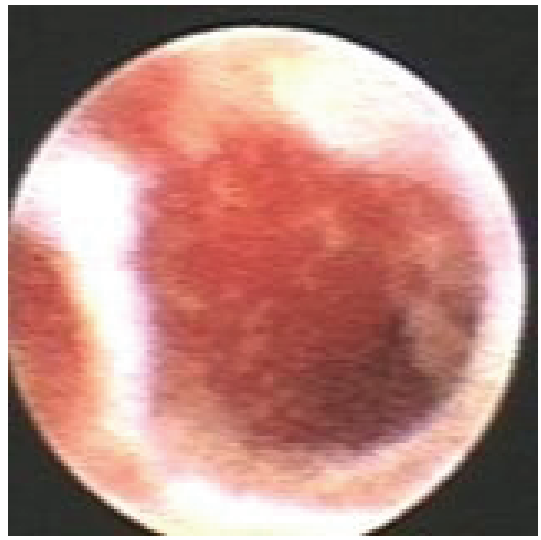

Figure 2: Appearances at mammary ductoscopy of DCIS.

Although the role of MRI in the management of DCIS is yet to be fully evaluated by randomised trials, it is being used to assess disease extent and distribution and to assess the contralateral breast [9, 10]. It is also used for early detection of invasive and noninvasive breast cancer in high-risk women [11]. A recent prospective observational study demonstrated MRI to be significantly more sensitive than mammography for the diagnosis of DCIS (92% versus 56%) [12].

MRI can overinterpret nonmalignant incidental lesions which may result in unnecessary interventions [13]. A recent retrospective report looking at MRI screening of high-risk women demonstrated an increased sensitivity of MRI for DCIS that was at least as good as the sensitivity for invasive disease [14]. This study examined two time periods (before 2001; 223 women and after 2001; 391 women) in one unit which used MRI and mammography to screen high-risk patients. After 2001, the unit acquired additional breast coils, better methods of data processing, and staff with appropriate specialist training. In the first period, 3.1% of screens were positive and 13% of these were DCIS. All were diagnosed by mammography. In the second period, 3.3% of screens were positive, 34% were DCIS. All of these were diagnosed by MRI and just one of these was also seen on mammography. The specificity of MRI was lower than mammography and significantly more patients were recalled for suspicious changes on MRI in the second study period than the first, but there was no significant difference in the numbers of biopsies performed.

Figure 1 shows regional ductal enhancement in the UOQ of the left breast anterior to a lumpectomy site in a 49-year-old female. This was recurrence picked up on screening MRI. Her mammogram was normal.

Mammary ductoscopy has been used to directly visualise DCIS. Figure 2 shows the appearance at mammary ductoscopy of histologically verified DCIS. However, this technique requires further investigation [15]. For example, it is limited by the fact that not all ducts are accessible from the nipple [16].

Currently, the preoperative diagnosis of impalpable lesions suspicious of DCIS requires either stereotactic or MRI guided core biopsy. Vacuum-assisted core biopsy (VACB) has been shown to increase the diagnostic yield and upgrade atypical ductal hyperplasia (ADH) to DCIS in approximately 25% of cases [17] and can be employed where standard core biopsy does not show DCIS yet the radiological changes are suspicious.

2. Pathological and Clinical Correlation

2.1. Classification. DCIS is defined by two features: firstly, the malignant epithelial proliferation is limited by the ductal basement membrane and secondly, stromal invasion is absent. DCIS behaves as a nonobligate precursor of invasive carcinoma and does not fully express the malignant phenotype [1]. The progression to invasive breast cancer is not completely understood and cannot be reliably predicted. Classification systems aim to reproducibly categorise lesions and to provide prognostic information to aid management decisions.

DCIS may be classified by grade, by architecture or morphology, by the level of differentiation, or by systems which use a combination of these factors [18].

Conventional histopathological types include comedo (tending to high grade cellular/nuclear features, often with central necrosis and calcification), solid, cribriform (with small holes or open spaces), and micropapillary (finger-like projections), however, lesions often demonstrate architectural and morphological heterogeneity [19, 20].

Cytonuclear grade is conventionally defined as low, intermediate, or high. It may vary between pathologists [21] and protocols have been developed to standardise reporting of grade [22]. Figures 3 and 4 show the characteristic features of low- and high-grade DCIS.

The "Comedo" subtype (high-grade, central confluent necrosis, and solid architectural pattern in >50% of the duct spaces) and the presence or absence of necrosis are important features and are incorporated into classifications such as the Van Nuys Index [23] and the Nottingham Grade [24].

All of the above classification methods as well as tumour size and the presence of absence of inflammatory changes

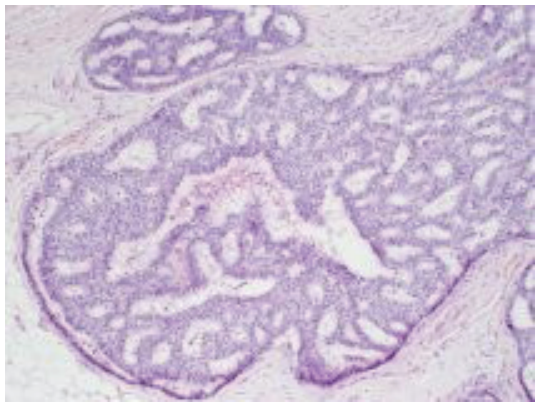

Figure 3: Low-grade DCIS.

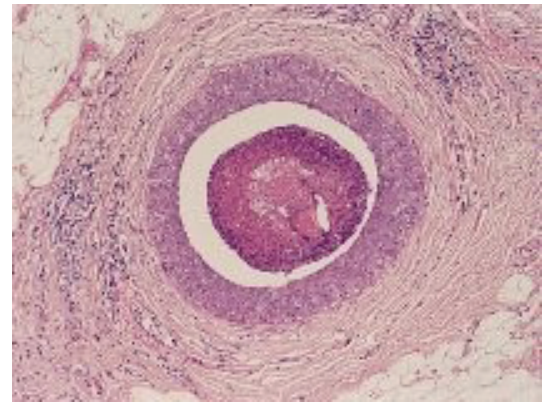

Figure 4: High-grade DCIS.

have been found to be statistically associated with the risk of local recurrence in an independent pathological review of cases from the UKCCCR/ANZ DCIS trial [18]. This indicates their independent value in the classification of DCIS. Their combination and weight in terms of prognosis is yet to be defined.

2.2. Natural History. The elusive natural history of DCIS probably reflects the biodiversity of the condition. Preinvasive lesions do not invariably progress to invasive malignancy [25].

The natural history of small, noncomedo, low-grade DCIS treated by biopsy alone has been evaluated in long-term followup studies. After a median of thirty-one years, 39% of patients developed invasive breast cancer, all of which occurred in the index quadrant and 45% of these patients died of metastatic disease [26]. The overall progression to invasive breast cancer has been reported to range from 14% to 75% [27].

There is a wide body of evidence on the risk factors for breast cancer overall, but evidence on risk factors specific to DCIS is limited. However, it does appear that the same factors are involved as for invasive disease; high mammographic density, significant family history of breast-cancer, age, obesity, and high lifetime exposure to oestrogens [11].

Hence, it would seem that patients who receive no treatment beyond a diagnostic biopsy remain at significant risk of progression to invasive disease and that DCIS represents a precursor of invasive cancer. Increased risk has been demonstrated in lesions of all nuclear grade. On the other hand, a significant proportion of DCIS lesions do not progress. As diagnostic frequency continues to increase, there is an impetus to accurately identify clinically relevant lesions in order to rationalise management.

2.3. Clinical Characteristics. Women with palpable DCIS and those who present symptomatically exhibit higher rates of LR than mammographically detected cases [28, 29]. Some screen-detected lesions may, therefore, be less relevant than symptomatic lesions [30].

One study identified a family history of invasive breast cancer as a significant predictor of LR in women with DCIS treated with BCS and RT [31]. Previous therapy with oestrogens, either contraceptives or hormone replacement therapy, is also reported to be a significant predictor of LR [32].

Young age (<40 years) has emerged as an independent risk factor for LR after BCS with or without adjuvant RT [33]. LR has been reported to range from 11–31% in this group, with the lowest rates in mammographically detected lesions [33].

2.4. Pathological Characteristics. A meta-analysis of 44 trials has reported significantly increased pooled risk estimates for local recurrence after treatment for DCIS if the disease is classified as "comedo" type, multifocal, if the lesion is large or highgrade. Involved margins were associated with the highest increase in risk estimates and there was limited evidence that ER- and PR-positive HER2 negative disease is less likely to recur [34].

In the meta-analysis, the pooled risk estimates for size were derived from 7097 women. Lesions greater than 20 mm in size were compared with lesions less than 20 mm. The risk estimate for larger lesions was 1.63 (95% CI 1.30–2.06). Accurate and reliable measurement of DCIS can be challenging and several landmark studies have been criticised for their performance in this regard [29, 35, 36]. The large numbers in the meta-analysis will have helped to mitigate this factor. The same study reported the summary risk estimate for multifocal versus unifocal disease to be 1.95 (95% CI 1.59–2.40) from analysis of 3895 patients [34]. It is possible that the total area of DCIS in multifocal lesions is greater than unifocal disease and that the difference in local recurrence could be secondary to this.

Involved margins are associated with an increase in LR, in patients treated by BCS alone, and in those who also undergo RT [37–39]. Consensus has yet to be reached with regard to optimal margin width [36]. The presence of DCIS at the surgical margin is associated with the identification of residual DCIS in 40–82% of reexcision specimens, and is correlated with margin width: 41% at <1 mm, 31% at 1-2 mm and 0% with ≥2 mm of clearance [40]. The French National Guidelines recommend surgical margins of ≥3 mm,

and reexcision for margins <1 mm [41]. A meta-analysis reporting the effect of margin status on local recurrence after BCS and RT concluded that a margin width of ≥2 mm was significantly superior to lesser margins (odds ratio (OR) = 0.53, 95% CI 0.26–0.96). However, there was no added value associated with clearance ≥2 mm compared to >5 mm (OR = 1.51, 95% CI 0.51–5.0) [42]. Despite this, total excision volume, independent of margin clearance, has also been correlated with LR. Following BCS for DCIS, the Joint Centre Experience reported LR rates at 5 years of 9% and 0% for volumes <60 cm^3, and >60 cm^3 respectively [43]. Excision volumes <60 cm^3 have been shown to increase the relative risk of LR in women under 45 years [33]. Margins were associated with the largest difference in the risk estimates for local recurrence in the meta-analysis by Wang [34]. The summary risk estimate for women with involved margins was 2.25 (95% CI 1.77–2.86).

High nuclear grade is associated with a greater risk of LR. In Wang's meta-analysis [34], 10,526 women were included in the analyses relating to grade, the summary risk estimate for high grade versus non-high-grade disease was 1.81 (95% CI 1.53–2.13).

The combination of nuclear grade and comedonecrosis is strongly associated with the risk of LR after BCS [23]. In the same meta-analysis of 9332 women with DCIS, the summary risk estimate of comedo-necrosis versus none for invasive breast-cancer recurrence was 1.71 (95% CI 1.36–2.16) [34].

A recent population-based case-control study found that comedo-type DCIS shares a similar profile of hormonal and reproductive risk factors to IBC, including ≥10 years of oral contraceptive intake and an inverse association with ≥3 full-term pregnancies. These findings were in contrast to those for noncomedo lesions, providing some further support for the differential management of DCIS lesions [44]. The significance of comedo-type as a risk factor for LR has resulted in its inclusion in prognostic indices [45, 46].

High-grade DCIS which is oestrogen receptor (ER) and progesterone receptor (PR) negative is significantly associated with HER2 and p53 positivity [47]. HER2 positivity and ER/PR negativity are individually associated with increased risk of LR [48]. HER2 overexpression represents an aggressive biological subtype of DCIS, correlating with high grade, p53 expression, and hormone receptor negativity. Hormone receptor positivity has been associated with low-grade DCIS. In a recent case series, HER2 was found to be superior to lesion size or nuclear grade in predicting concurrent invasive disease. DCIS that overexpressed HER2 was 6 times more likely to be associated with invasive disease (OR 6.4, $P = 0.01$) [49].

In the Wang meta-analysis [34], higher rates of local recurrence were seen in ER/PR negative, HER2, positive-patients but the differences were not statistically significant.

2.5. Molecular Characteristics. Various molecular markers have been studied in DCIS as possible predictive or prognostic factors for progression to invasion or for the development of invasive recurrences.

In invasive breast cancer, classifications based on biological profile (derived from gene profiling and correlated with immunohistochemical profile) rather than morphology have been developed and shown to correlate with prognosis. In order; Luminal A, Luminal B, Triple negative, and Basal Type invasive breast cancers are associated with a worsening prognosis [50]. The same profiles have been demonstrated in DCIS [51]. More work is now needed to establish whether these profiles influence the likelihood that an area of DCIS will progress.

Chromosome-wide comparative genomic hybridization has shown DCIS to be a genetically advanced lesion with alterations corresponding to adjacent invasive disease and independent pathways of genetic evolution [52]. A distinctive molecular portrait of each lesion can be obtained by gene expression profiling using complementary DNA microarrays [53].

One such study has identified a gene expression classifier of 35 genes which differ between DCIS and IBC and a further 43 genes distinguishing well-from poorly differentiated DCIS [54]. Protein expression profiling can similarly be undertaken using matrix-assisted laser desorption/ionization (MALDI) or surface-enhanced laser desorption/ionization (SELDI). Although the relevance of each parameter may not be fully understood, combinations of features may enable the biological profiling of DCIS lesions into groups of similar natural history and prognosis.

Balleine et al. recently reported on a binary molecular grading scheme for DCIS, based on expression at 173 oligonucleotide probes. Two conventional parameters amenable to routine evaluation (nuclear grade and Ki67 score) were capable of accurately assigning lesions into low or high molecular grade [55].

Proteomics analysis of DCIS and normal breast tissue has also identified differential expression patterns, distinct from previous nucleic-acid-based studies [56]. Expression of Syndecan-1, E-cadherin, and c-met have recently been shown to be associated with angiogenic and lymphangiogenic factors in DCIS, including endothelin A and B receptors, vascular endothelial growth factor (VEGF)-A/C, and fibroblast growth factor receptor (FGFR)-1 [57]. In addition to their potential use for prognostication, putative molecular targets may enable directed therapy in the future.

Intuitively, molecules such as matrix-metalloproteinases (MMPs) and tissue inhibitors of matrix-metalloproteinases (TIMPs) that influence the invasion of stroma and basement membrane should be important in the progression of DCIS to invasive breast cancer. Significantly different expression profiles of MMPs and TIMPs have been noted in DCIS, admixed DCIS, and invasive breast cancer [58]. More work is needed to understand the role these molecules have in progression to invasive cancer but their expression profiles could help determine lesions that should be treated more aggressively.

3. Management

It is possible that not all DCIS needs to be treated aggressively as not all DCIS will become invasive. In particular, small,

low-grade lesions detected by screening may fit into this group. Management strategies need to consider the breast and axilla, the need for adjuvant RT, and the role of systemic adjuvant therapy. Treatment of the breast can involve BCS (with or without RT) or mastectomy (Mx). Axillary surgery, even SLNB, warrants particular caution in view of their low yield and potential for harm. Adjuvant systemic treatments have mainly involved oestrogen blockade with Tamoxifen. The optimal management of DCIS remains controversial [59].

3.1. Surgery. Complete excision of DCIS with clear margins is the most important factor in reducing the risk of LR. Mx is indicated for large tumours (>4 cm depending on breast size), multicentric lesions, inadequate margins after BCS, local recurrence after BCS (particularly with prior RT), and patient preference. Mx affords excellent local control, approximately 98% at 7 years, with an overall recurrence rate of 1.5% [60].

In England and Wales between 1990 and 2001, the absolute number of mastectomies for *in situ* disease increased by 400%, corresponding to the introduction of national screening [61]. The relative rate of Mx for DCIS has been decreasing over the last three decades and the procedure is now undertaken in approximately one third of patients [62]. The French Survey reported Mx rates of 10% for lesions <10 mm compared to 72% for >20 mm, and 11% for low-grade compared to 54% for high-grade lesions. The authors justify an Mx rate of 50% for patients <40 years by the lifetime risk of LR in those undergoing BCS despite adjuvant RT [62].

If patients do require Mx for DCIS, an immediate breast reconstruction is relatively uncomplicated as postmastectomy radiotherapy and lymph node dissection will not be required [63].

BCS combined with RT is an acceptable treatment option for smaller, unifocal areas of DCIS. There is probably not enough evidence to justify BCS without RT routinely. Significant numbers of patients undergoing BCS alone develop LR, of which approximately half are invasive and up to one fifth ultimately metastatic. The literature reveals an overall LR rate of approximately 28% at 7 years, around 45% of which are invasive [37–39, 64–68]. There is also evidence that mammographically detected DCIS treated by BCS alone has unacceptable rates of LR (10-year LR rates were 27.8%, 22%, and 19%, resp., of which approximately 35% were invasive) [68–70].

3.2. Radiotherapy. The benefit of adjuvant RT, in terms of reduced LR in those undergoing BCS, has been demonstrated by several large randomized controlled trials. However, clear margins are necessary even if RT is given to obtain acceptable rates of LR [37, 38, 71, 72]. There remains a lack of level-1 evidence supporting the omission of adjuvant RT in selected low-risk cases.

The National Surgical Breast and Bowel Project (NSABP B-17) trail randomized 818 patients after BCS surgery for DCIS, to either whole breast RT or no further treatment [35]. After a median followup of 129-months, of the 403 women treated by wide local excision alone, there were 124 local recurrences (31.7%), 67 of which were invasive (54%). Of the 410 women treated by wide local excision and RT, 61 local recurrences were observed (15.7%) of which 29 were invasive (48%, $P = 0.001$). Despite the fact that RT was associated with a 57% reduction in LR (both invasive and *in situ*), no differences were observed in the rates of distant recurrence and overall survival.

An analysis of long-term data from the NSABP B-17 and NSABP B-24 trials [73] showed that at 15 years the radiotherapy treated patients still had significantly fewer local recurrences and this effect had increased over time. Of those that did recur, 54% were invasive, and for these patients, overall survival was lower (HR of death = 1.75, 95% CI = 1.45 to 2.96, $P < 0.001$).

The European Organisation for Research and Treatment of Cancer (EORTC) conducted a similar study recruiting 1010 patients [29]. After a median followup of 126 months, local relapse-free rates were 85% in the RT group and 74% in the control group (HR: 0.53, $P < 0.0001$). *In situ* LR rates were 7% and 13%, respectively, and invasive LR rates were 8% and 13% respectively [74]. Consistent with the NSABP B-17 trial findings, the absolute reduction of LR by RT increased with time from 7% at 4 years to 11% at 10.5 years. In univariate analysis, RT showed a statistically significant benefit in all subgroups of patients, but the size of this benefit varied. The authors observed a 23.5% and 42.7% LR rate for complete and incomplete/doubtful excisions, respectively, in the lumpectomy alone group, versus 14.7% and 24.7% for patients receiving adjuvant RT. Indicating the importance of clear margins even with RT.

The UK/ANZ DCIS trial involved 1701 patients treated by BCS, with subsequent randomisation to RT and/or Tamoxifen [75]. There were four treatment groups: BCS alone, BCS + RT, BCS + TAM, and BCS + RT + TAM. 90% of the participants were 50 years or older with screen detected DCIS. After a median followup of 53 months, the respective rates of LR were 22%, 8%, 18%, and 6%. Adjuvant RT was associated with a significant reduction (hazard ratio (HR) = 0.38, $P < 0.0001$) in all ipsilateral tumour recurrence (invasive or DCIS). RT reduced the risk of DCIS by 64% ($P = 0.0004$) and invasive cancer by 55% ($P = 0.01$). Long-term followup data has since been reported for this trial [76]. At a median followup of 12.7 years, the treatment effects are similar in magnitude.

The Cochrane Collaboration has recently published a systematic review of four adjuvant RT trials: NSABP 2001 [35], EORTC 2006 [29], UK/ANZ DCIS 2003 [75] and the Swedish DCIS 2008 [77]. With regard to LR, they report a 51% pooled risk reduction for DCIS (HR 0.61, 95% CI 0.39–0.95, $P = 0.03$) or invasive cancer (HR 0.50, 95% CI 0.32–0.76, $P = 0.001$). After a median followup ranging from 4.4–10.5 years, the LR rate for those receiving RT was 11.6% compared to 23.9% for BCS alone, resulting in a number needed to treat (NNT) of 9 patients to prevent one LR. Although there was no attributable increase in mortality, long-term RT complications were poorly reported by the trialists [78].

A further meta-analysis also concluded that adjuvant RT significantly reduces the risk of LR after BCS—by approximately 60%, with most benefit to patients with high-grade lesions and positive margins. RT did not significantly alter the rate of distant metastases or overall survival [79].

Overall, LR rates have been reported to range from 2.7% to 18.9%, averaging 10% at 7 years, with invasive LR accounting for approximately 60% [80]. However, the methodological quality of several trials has been criticised, particularly in terms of the treatment of unclear margins, the methodology and design of the studies, and the validity of conducting posthoc secondary retrospective analyses [29, 35]. Whilst some of these issues can be resolved by meta-analysis, others are being addressed by current studies.

Although it has been long been proven that radiotherapy after mastectomy for invasive breast-cancer reduces local recurrence [81], good evidence that this in turn leads to reduced mortality took much longer to be published [82, 83]. DCIS is associated with a better prognosis than invasive breast cancer and, therefore, proof of a survival benefit with radiotherapy may take time to establish.

Strategies such as a boost of RT to the tumour bed are used in IBC. There is no evidence that this reduces LR in DCIS. A study of 75 patients treated by BCS+RT, including 20 women receiving an additional 10 Gy boost to the tumour bed, identified no improvement in LR reduction after a median followup of 81 months [84]. The efficacy of other novel strategies including partial breast RT in the context of DCIS has yet to be evaluated [71, 72, 85]. Accelerated partial breast irradiation (APBI) aims to provide comparable local control to whole-breast RT with reduced morbidity. In the largest study group of patients with DCIS ($n = 194$) treated with the MammoSite device, the 3-year actuarial LR rate was 0% in the first 48 cases enrolled compared to 2.04% in IBC ($n = 352$); median followup 37.5 months [86]. Another recent study of 126 DCIS cases evaluated balloon-based brachy therapy, with either MammoSite or Contura catheter. After a median followup of 40 months, the LR rate for the first 50 consecutive cases was 0.02% with a 3-year actuarial rate of 2.15% [87].

The ECOG group (Eastern Cooperative Oncology Group) prospectively studied 565 nonrandomised patients with single areas of DCIS less than 2.5 cm in size treated by breast conserving surgery alone, with margins of greater than 3 mm and split these patients into a low and intermediate group versus a high-grade group [88] attempt to determine a sub-group of patients in whom RT could be omitted. After a median followup of 6.7 years, the local recurrence rate was 6.1% (95% CI: 4.1–8.2%) in the low to intermediate grade group and 15.3% (95% CI: 8.2–22.5%) in the high grade group. On the basis of this, the authors suggest that small, low-grade lesions excised with generous margins by breast-conserving surgery may not need radiotherapy. The authors did caution that longer followup and additional study would be needed to confirm this and raise the point that recurrences from low-grade lesions may present later.

The Radiation Therapy Oncology Group trial (98-04) was a randomised trial designed to assess the need for radiotherapy for DCIS in patients with "low-risk" but unfortunately closed due to nonaccrual. A recent study attempted to account for the nonrandomisation in the ECOG DCIS study by comparing two groups of patients (low and intermediate or high grade DCIS) that were treated with breast-conserving surgery and radiotherapy with the two groups in the ECOG study [89]. In these 263 patients, with similar length of followup, there was a reduction of more than 70% in the local recurrence rates with radiotherapy.

More evidence is needed to confirm if there is a subgroup of patients with DCIS that do not need radiotherapy after breast conservation.

3.3. Endocrine Therapy. Hormonal therapies (mainly Tamoxifen) are the main stay of systemic adjuvant therapy in DCIS.

The NSABP B-24 trial was designed to assess the benefit of Tamoxifen for 5 years versus placebo after BCS and RT for DCIS [90]. After 7 year median followup, the LR rates were 11.1% and 8% in the placebo and Tamoxifen groups, respectively ($P = 0.02$). The absolute reduction was significant for invasive LR. There was a significant excess of endometrial cancer and thromboembolic events in the Tamoxifen group. No significant benefit was observed in the following groups: age >50 years, *in situ* LR, complete local excision, and absence of necrosis. The overall mortality was not affected [91]. A posthoc analysis of ER status demonstrated that efficacy was limited to the 77% of cases which were ER positive [92].

The UK/ANZ DCIS trial also assessed the effect of adjuvant treatment with Tamoxifen after BCS and RT for DCIS. The results were originally reported after a median followup of 4.4 years [75]. At this point, there was no significant difference in the incidence of invasive breast cancer events in the Tamoxifen-treated patients. However, the total number of DCIS events (ipsilateral and contralateral) was significantly reduced by Tamoxifen (6% versus 10%, $P = 0.03$). After a median of 12.7 years followup [76], a significant difference in all new breast events in Tamoxifen treated patients was seen (HR 0.71, 95% CI 0.58–0.88; $P = 0.002$). Tamoxifen reduced both recurrent ipsilateral DCIS (HR 0.70, 95% CI 0.51–0.86; $P = 0.03$) and contralateral tumours (HR 0.44, 95% CI 0.25–0.77; $P = 0.005$). No significant reduction in ipsilateral invasive disease has been proven (HR 0.95, 95% CI 0.66–1.38; $P = 0.8$).

There is, therefore, good data that Tamoxifen reduces local recurrence and the risk of contra-lateral tumours in DCIS treated by BCS and RT. Some DCIS is probably low-risk enough to omit it, but clear evidence on this is lacking.

There is currently only limited data on the use of aromatase inhibitors in DCIS.

Trials are ongoing to determine if Aromatase inhibitors are superior to Tamoxifen in the adjuvant setting after breast conserving surgery for DCIS (NSABP B-35 and IBIS II).

Recently, inhibition of cyclo-oxygenase 2 (COX-2), implicated in epithelial-stromal interactions and promoting the progression of DCIS, has been evaluated using nonsteroidal anti-inflammatory drugs (NSAIDS). Results from

experimental studies were encouraging [93, 94] but were not supported by the ERISAC trial [95].

3.4. Sentinel Lymph Node Biopsy. Pure DCIS does not exhibit lymphatic or vascular invasion so surgical staging of the axilla is not necessary [59]. However, lesions thought to be noninvasive on core biopsy are upgraded in 10–33% of cases on final postoperative histology [96, 97] and lymph node positivity has been reported in 1-2% of patients (20) (which may be attributable to "missed" invasive foci) [27]. A relative indication for SLNB in DCIS is patients undergoing Mx, as these patients are likely to have risk factors for occult invasion—large or multifocal lesions, high-grade, mastectomy for recurrent disease [97].

Retrospective analyses from the NSABP B-17 and B-24 trials support the strategy of avoiding routine axillary surgery in DCIS due to low yield and risk of morbidity [98, 99].

3.5. Local Recurrence. If LR occurs after DCIS, it may be *in situ* or invasive. It occurs at the site of the original lesion or within the index quadrant in 75–80%. The risk decreases as the extent of primary treatment increases (BCS, BCS + RT, Mx). Ironically, LR can be more aggressive in those who were treated more aggressively. Whereas 40–50% of LR is invasive after BCS, LR is almost always invasive following Mx. This may reflect the fact that recurrence after BCS often presents as an incidental finding of *in situ* disease during surveillance mammography, whereas postMx ipsilateral mammographic screening is obviously not undertaken and recurrence is likely to present at a more advanced stage and relies on clinical detection [100]. The prognostic implications of invasive LR are significantly worse than *in situ* recurrence. In particular, the overall risk of metastasis has been reported to be 0–3.6% for *in situ* LR, compared to 13.2–18% after invasive LR [37, 38, 71, 72, 101]. The rate of axillary lymph node involvement with invasive LR ranges from 11–30% [37, 38, 71, 72].

Completion Mx is indicated following LR within the breast when reexcision would be cosmetically unacceptable, or when LR is confirmed to be invasive and for those with an absolute or relative contraindication to RT (i.e., previous adjuvant RT). In the NSABP B-17 trial, the Mx rate for LR was 48% in the BCS group and 62% in the BCS + RT group [35], consistent with similar studies reporting rates of 52.8% and 74.7%, respectively, [37, 38]. Overall, salvage Mx rates range from 64–84% [37, 38, 71, 72].

3.6. Special Clinical Scenarios. Management of the elderly DCIS patient (particularly those over 70 years) is not strongly evidence based as this group has often been excluded from important trials and screening programs [35, 45, 46, 71, 72, 90, 91].

Women exposed to thoracic radiation, including prior treatment for haematological malignancies, are at risk of developing secondary tumours, with breast cancer representing the most common solid lesion and DCIS accounting for 11–17.7%. The risk is significantly increased at adolescence and young adulthood with a median onset interval of 16 years. In one study, the majority of these patients were treated with Mx, however, 29% underwent BCS ± RT [102].

Male DCIS has been reported in approximately 300 cases, however, the incidence of DCIS within IBC ranges from 0% to 17% with an average of 7% [103, 104]. Patients may present with a subareolar mass, Paget's disease, or serosanguineous nipple discharge. Optimal control is achieved with simple mastectomy and lumpectomy alone has been associated with a higher rate of LR.

3.7. Future Strategies. Minimally invasive interventions for breast cancer seek to redress the balance between benefit and risk and may, therefore, be of particular use in asymptomatic patients with low-risk lesions or patients deemed unfit for conventional management. Image-guided radiofrequency ablation therapy (RFA) has been demonstrated in pilot studies to be effective with few complications and a favourable safety profile. However, complete ablation may not achievable in all patients and exhaustive histological specimen analysis is not possible. Furthermore, current imaging modalities are relatively imprecise at delineating the extent of DCIS and predicting/confirming complete ablation [105].

4. Summary

DCIS should be managed within the multidisciplinary team and management tailored to patient and tumour factors. Local control depends upon adequate surgical clearance, and in order to reduce the risk of LR, surgical margins of at least 2 mm should be achieved. SLNB can be considered in patients with a high-risk of occult invasive disease. RT following BCS significantly reduces LR, particularly in those at high-risk. There remains a lack of level-1 evidence supporting the omission of adjuvant RT in selected low-risk cases. Large, multicentric, or recurrent lesions (particularly in cases of prior RT) should be treated by Mx and immediate reconstruction should be discussed. Adjuvant Tamoxifen may reduce the risk of LR in patients with hormone sensitive disease. Further research is required to determine the role of contemporary RT regimes and endocrine therapies. Biological profiling and molecular analysis represent an opportunity to improve our understanding of the tumour biology of this condition and rationalise its treatment. Reliable identification of low-risk lesions could allow treatment to be less radical or safely omitted.

5. Search Strategy and Selection Criteria

Articles were identified by searches of Medline, PubMed, Embase, and Cochrane databases up to September 2011 using the terms: "DCIS" or "ductal carcinoma *in situ*" and "treatment" or "management" or "surgery" or "radiotherapy" or "radiation" or "mastectomy" or "sentinel lymph node biopsy" or "natural history" or "Tamoxifen" or "recurrence" or "invasive." Studies identified were screened for those that focused on DCIS treatment. All randomized controlled trials and large retrospective series were included.

The references in this review were selected to provide a balanced and representative overview of a complex subject with an extensive base of published work.

Conflict of Interests

The authors declared no conflict of interests.

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Review Article

Investigational Paradigms in Downscoring and Upscoring DCIS: Surgical Management Review

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Counseling patients with DCIS in a rational manner can be extremely difficult when the range of treatment criteria results in diverse and confusing clinical recommendations. Surgeons need tools that quantify measurable prognostic factors to be used in conjunction with clinical experience for the complex decision-making process. Combination of statistically significant tumor recurrence predictors and lesion parameters obtained after initial excision suggests that patients with DCIS can be stratified into specific subsets allowing a scientifically based discussion. The goal is to choose the treatment regimen that will significantly benefit each patient group without subjecting the patients to unnecessary risks. Exploring the effectiveness of complete excision may offer a starting place in a new way of reasoning and conceiving surgical modalities in terms of "downscoring" or "upscoring" patient risk, perhaps changing clinical approach. Reexcison may lower the specific subsets' score and improve local recurrence-free survival also by revealing a larger tumor size, a higher nuclear grade, or an involved margin and so suggesting the best management. It seems, that the key could be identifying significant relapse predictive factors, according to validated risk investigation models, whose value is modifiable by the surgical approach which avails of different diagnostic and therapeutic potentials to be optimal. Certainly DCIS clinical question cannot have a single curative mode due to heterogeneity of pathological lesions and histologic classification.

1. Introduction

1.1. Biopathological Profile. Ductal carcinoma in situ (DCIS) represents a heterogeneous group of proliferations varying in cytological and architectural appearance, for some of which it is believed that there are major clinical consequences [1]. Some studies have documented the sharing of molecular and genotypic characteristics in different benign and malignant stages of progression. Comparative analyses for implementing predictive markers in tumour biology show a multitude of genetic alterations in all the DCIS cases and propose distinct pathways in morphological evolution (poor, intermediate, and well). Poorly differentiated diseases displayed a higher frequency of amplifications (17q12, 11q13) and a higher average rate of genetic imbalances (40%) suggesting a developmental progression model for intraductal carcinoma [2]. Although the biological impact of these findings is not yet known, it is likely that DCIS differs by genetic grading and thus in prognostic implications. In fact the main question relating to the treatment is whether to consider DCIS a direct precursor of invasive cancer [3]. The natural history of small, noncomedo, and low grade in situ lesions treated by biopsy alone has been evaluated in studies with long-term follow-up. In the series reported by Sanders et al. 11 of 28 women (39.3%) have developed invasive breast carcinoma (IBC) after a median of thirty-one years, and 5 of 11 women (45%) died of metastatic disease [4]. In similar findings the risk of invasive disease has been described in a range of 14–75% of cases confirming a total progression impact of 43%. This has led to a rapidly consensus that atypical intraductal hyperplasia (AIDH) indicates a small, generalized, increased risk of breast carcinoma in both breasts that is approximately one half of low-grade DCIS lesions [5]. In our opinion, a practical difference between these diagnoses leads to a deeper level of understanding the rational therapeutics but it is also one of the most critical intersections of histopathology and

clinical management today. With the diagnostic increase, the aim is to accurately identify clinically relevant lesions and streamline the treatment strategies. This emphasizes the significance of conceiving a less aggressive therapy (local excision only) when these lesions are limited in size, and the recurrence interval may well be beyond a reasonable life expectancy for the patient.

2. Evolving Knowledge

2.1. Critical Insights into Epidemiology. Percentage of carcinoma in situ (including DCIS and LCIS) from cancers diagnosed in the arm of selected screening studies now accounts for about 20–25% of all cases and from 17 to 34% of mammography detection [6].

In the United States, DCIS incidence rose from 1.87 per 100000 in 1973–1975 to 32.5 in 2004 [3]. Data from the Surveillance and End Results program depict about a 500% increase in DCIS among women aged 50 years and older from 1983 to 2003 with incidence starting to decline in 2003. An opposite trend has been verified among younger women in whom there has been a 290% increase since 1983 and the incidence continues to rise [7]. In addition, the prevalence of comedo subtype has not increased as rapidly as the less aggressive forms across all age groups. An analysis based on cancer registries found that between 1991 and 2001 the age-adjusted incidence of comedo DCIS was unchanged at approximately seven per 100000 rose from 16.5 to 31 per 100000 for noncomedo lesions [8]. The actual prevalence in the population is difficult to estimate because most patients are asymptomatic [7], but an improved understanding of information regarding frequency and risk factors could lead to critical insights into biological implications.

2.2. Classification Debate. Different classification systems may have important implications in clinical and prognostic management. No single scheme has been universally accepted and experts disagree as to which is the most appropriate [9].

The problem areas consist of the difficulties in separating low-grade DCIS from atypical intraductal hyperplasia (AIDH) and accurately defining disease size and extent. Moreover, due to the subjective interpretation of architecture and predictive features such as nuclear grade, necrosis, and polarization, many experienced pathologist differ in their diagnosis of DCIS [10].

According to the European Pathologist Working Group (EPWG) classification (G1, G2, G3), adopted by the European Organization for the Research and Treatment of Cancer (EORT), all the lesions are divided into three classes reflecting a statistically different association between nuclear grade and recurrence (P.009) [11].

The Van Nuys Prognostic index (VNPI) was developed to aid in the complex treatment selection process also including age, tumor size, and margin width to place patients in categories corresponding to clinical algorithms (Table 1). Pathological classification combines high nuclear grade and comedo-type necrosis to predict clinical behavior and stratify disease into three groups: non-high-nuclear grade without comedo-type necrosis (Score 1), or with necrosis (Score 2) and high nuclear grade (Score 3).

Silverstein et al. recently reported 31 local recurrences in 238 patients after breast-conservation surgery, 3.8% (3/80) in group 1, 11.1% (10/90) in group 2, and 26.5% (18/68) in group 3. The 8-year actuarial disease-free survivals were 93%, 84%, and 61%, respectively (all $P \leq 0.05$) [1]. However, according to our experience, tissue processing by the Van Nuys protocol is complex, thus limiting its feasibility in clinical practice.

Traditionally, highly heterogeneous intraductal proliferative lesions have been subdivided into noncancer—intraductal hyperplasia (IDH) and atypical intraductal hyperplasia (AIDH)—and cancer—DCIS, grades 1, 2, and 3. According to Tavassoli FA viewpoint a recognized problem with current classification is the interobserver variability and lack of reproducibility in lesions assignment with similar morphologic, immunohistochemical, and molecular characteristics. There is, for example, no justification in separating AIDH from low-grade DCIS because of their simply differences in size and quantity [10].

Moreover, the possibility of misunderstanding florid ductal hyperplasia is also really concrete. A review of 350 DCIS by expert breast pathologists resulted in a change in treatment recommendations in 93 (43%) cases and a conclusion that an expert assessment is necessary in this context [12].

According to Tavassoli the designation of carcinoma in situ is to be abandoned and it is necessary to unify the intraductal proliferations or alterations under the designation of ductal intraepithelial neoplasia (DIN) lesions that constitute risk factors for subsequent development of invasive carcinoma. There are three DIN categories, DIN-1 to DIN3. DIN-1 includes IDH (grade 1a), AIDH (grade 1b), and grade 1 DCIS (grade 1c); DIN-2 includes grade 2 DCIS; DIN-3 includes grade 3 DCIS [13].

In fact O'Connell et al. in the most comprehensive assessment of loss of heterozygosity (LOH) among intraductal proliferations showed that LOH of at least one genetic locus was shared with the synchronous invasive cancer in 37% of 19 patients with usual ductal hyperplasia (IDH), 45% of 11 patients with AIDH, 77% of 13 patients with non-comedo DCIS, and 80% of 11 patients with comedo DCIS [14].

In conclusion, DIN system offered a translational table for conversion of the currently used terminology of DCIS. This could lead to decrease impact of having two drastically different designations of cancer (DCIS) and noncancer (AIDH) applied to same lesions, caused by interobserver variability, reducing also geographically the term cancer-related overtreatment possibilities.

However, there are limitations to this classification, such as the inclusion of IDH among neoplasias, that may cause undue concern for those not aware that a tumor can be totally benign.

We think that analyzing with emphasis the areas of controversy and exciting new research prospects could enhance consistency in the interpretation and reporting of such complex and challenging disease.

Table 1: The USC/VNPI scoring system.

Van Nuys Prognostic Index			
Parameter	Score 1	Score 2	Score 3
Van Nuys Classification	Group 1	Group 2	Group 3
	Non high nuclear grade without necrosis	Nonhigh nuclear grade with necrosis	High nuclear gradewith or without necrosis
Margins	≥10 mm	1–9 mm	<1 mm
Size	<15 mm	16–40 mm	>40 mm
Age	>60	40–60	<40

Modified from Silverstein; Ductal Carcinoma in situ of the breast 2nd ed. 2002.

Table 2

Author and reference	Parameter	Results	
Ottesen et al. [15]	Size	10-year LR rates of DCIS treated by BCS alone ($n = 275$)	
	<10 mm	LR 11%	
	>10 mm	LR 48%	
Cutuli et al. [29]	Size	5-year LR rates of BCS versus BCS + RT groups ($n = 1,289$)	
	<10 mm	LR 30%	LR 11%
	>10 mm	LR 31%	LR 13%
Dunne et al. [18]	Margin	Optimum margin threshold for DCIS resection ($n = 2,514$)	
Number of patients	Negative Margin Width	Percentage of patients with IBTR (5-year follow-up)	
914	No cells on ink	9.4	
1,239	1 mm margin	10.4	
207	2 mm margin	5.8	
154	≥5 mm margin	3.9	
Kerlikowske et al. [57]	Nuclear Grade	Invasive LR rates of DCIS treated by BCS alone ($N = 1491$)	
MacDonald et al. [43]			
	Low-grade lesions	6%	
	High-grade lesions	31.5%	
Silverstein et al. [1]	VNPI Score	LR rates and DFS in three groups of DCIS patients ($N = 238$)	
(1) Non-high-grade DCIS without comedo-type necrosis		3.8%	93%
(2) Non-high-grade DCIS with comedo-type necrosis		11.1%	84%
(3) High-grade DCIS with or without comedo-type necrosis		26.5%	61%

2.3. Pathological and Predictive Features. In view of the increasing number of patients treated with breast conserving treatment (BTC) for ductal carcinoma in situ, risk factors for recurrence and metastasis should be identified (Table 2).

The size of DCIS lesions has been correlated with LR but several studies have been criticized for performance in this regard.

Results by Ottesen et al. after 10-year follow-up reported a local recurrence (LR) rate of 11% and 48% for lesions smaller and larger than 10 mm, respectively, showing a significant association with a specific threshold [15]. However these findings were not supported by the French Cancer Centre's experience which identified LR rates of 30% and 31% in BCS group for lesions under or over 10 mm respectively, and 11% and 13% for the same subgroups in the BCS + RT group [16].

Surgical clearance is considered the most important risk factor for local recurrence and consensus has yet to be reached about optimal margin width. On univariate analysis Neuschatz et al. found that margin width and lesions size of initial excision specimens are significantly predicted for the presence of residual DCIS on reexcision. Residual tumor was found on reexcision in 41% of greater than 0-1 mm, 31% of greater than 1-2 mm, and 0% of greater than 2 mm clearance ($P < 0001$) [17].

In fact inadequate margins may result in high local recurrence, and excessively large resections may lead to poor cosmetic outcome without oncologic benefit.

In a recent meta-analysis when a 5 mm or greater margin was compared with a margin of 2 mm, no significance difference in the risk of IBTR (3.8% versus 5.8%) was observed (OR = 1.51; 95% CI, 0.51 to 5.04; $P > .05$). However, when specific margin threshold was examined, a 2 mm margin was found to be superior to a margin less than 2 mm (10.4%; OR 0.53; 95%CI, 0.26 to 0.96; $P < .05$) [18].

Women with high nuclear grade DCIS or clinical exhibition treated by lumpectomy may be appropriate candidates for additional treatment.

Studies of DCIS treated by BCS alone have reported LR rates ranging from 6% for low grade up to 31.5% for high-grade lesions [19].

Ottesen et al. supported the consideration of large cell/high grade DCIS as a biologically aggressive lesion with high recurrence rate and confirmed a low malignant potential with low failure rate at short-term follow-up and a delayed pattern of development for small and low type [15].

Histopathologically, in DCIS a strong association was found between large nuclear size and comedonecrosis as independent significant predictors. The recurrence rate among the high-grade/comedo-type lesions was 40%, 47%, 19%, and 33%, respectively, in different series treated by BCS alone [20–23]. The significance of comedo-type as a risk factor for LR has resulted in its inclusion in prognostic indices. The Van Nuys classification combines both features to define three distinct groups with predictive utility after BCS and facilitating clinical decision making [24].

3. Management

3.1. Clinical Practice. Based on the results of the several studies it is clear that DCIS represents a broad spectrum of disease and a uniform approach to treatment is not appropriate. Some patients require no treatment other than excision alone, others benefit from complete excision plus radiation therapy, and some will require mastectomy [25].

The challenge is using available clinical and pathologic data to define therapy for specific subsets of risk and quantify the evolving knowledge of prognostic factors.

Management strategies need to consider the breast and axilla, the need for adjuvant RT, and the utility of systemic adjuvant therapy. The gold standard in surgical treatment includes oncological radicality, optimizing cosmetic results with a positive psychological outcome. Today, through the joint activities of a multidisciplinary team and scientific expertise a uniform operating pattern is searched, but despite these general principles, the optimal management of DCIS remains controversial [5, 26].

3.2. Radical Treatment. Despite the significant transition from symptomatic patients toward those with screen detected pathology, paradoxically in some cases DCIS is managed with the radical intent applied to invasive breast cancer (IBC) [27]. Douek and Baum determined the impact of England screening on the type of surgery undertaken and reported an increase of 373% in the number of operations performed for DCIS and of 422% for the mastectomy practice over a period of 11 years [28].

In the French survey experience mastectomy (MX), conservative surgery alone (CS) and CS with radiotherapy (CS + RT) were performed in 30.5%, 7.8%, and 61.7% of 1289 patients, respectively (Table 3) [29].

Although the data indicate a sharp decline in the procedure rate, given the dramatic increase in the number of diagnoses, the actual incidence of MX at 7.8 per 100000 women did not change, and several studies confirmed an approximately application in one-third of cases. General guidelines recommend that patients with extensive or multifocal DCIS involving 4-5 cm of disease or more than one quadrant should be offered mastectomy. Moreover, women with potential contraindications to breast irradiation or a strong preference for mastectomy over breast conservation have been considered appropriate candidates for this procedure. The risk of a radical intervention is defined higher in some clinical scenarios like diffuse and suspicious-appearing microcalcifications, suboptimal tumor to breast size ratio with an unacceptable cosmetic results, the inability to obtain margin control by lumpectomy or reexcision(s) [30].

In the French survey the authors did not assess multifocality and multicentricity but analyzed the notion of residual tumor on the specimen in case of multiple surgery, maximal tumor size, and final margin status to predict the best surgical option (especially mastectomy). This study reported MX rates of 10% for lesions <10 mm compared to 72% for >20 mm, 11% for low-grade compared to 54% for high-grade lesions, and 43% for comedo carcinoma against 28% of other pathological subtypes [29].

The comparison of data in patients treated with MX and BCS showed a significant improvement in local control obtained with mastectomy (relapse free rate of 98.2% versus 89.7% at 10 years $P = 0.02$) without obvious impact on survival (98.7% in both groups) [31].

Thanks to the advances in diagnosis and improvements in reconstructive surgery, mastectomy will continue to be an important and acceptable treatment option in some cases. Cutulli et al. results confirm a 98% local control rate as reported by other series. After a 91-month median follow-up, local recurrence (LR) rates were 2.1, 30.1, and 13.8% in the MX, CS, and CS + RT groups of 716 women. The importance of case selection is discussed in relation to the high invasive recurrence rate following conservative surgery with (LR 59%) or without radiotherapy (LR 60%) and relative reported incidence of metastases reported in this subgroup (19%) [32] (Table 4).

Furthermore, among all surgically treated patients the cumulative risk of contralateral disease increased with an annual rate of 0.6% and some women undergo prophylactic mastectomy (CPM) to prevent cancer in the opposite breast. A recent surge reported a progression of CPM rate from 2.1% to 5.2% between 1998 and 2005, and factors contributing to this change most certainly include improved reconstructive outcomes and more widespread use of magnetic resonance [33].

Various approaches for radical surgery are currently used and include simple mastectomy (excision of breast tissue and

Table 3: Treatment modalities according 1289 DCIS patients.

Breast surgery	CS 7.8%	CS/RT 61.7%	MX 30.5%
	(France)	Range (84–96%)	Range (20–37%)
	(United States)	Range (39–74%)	Range (26–45%)
Axillary surgery	SLNB 21.3%	AD 10.4%	
Hormonal therapy	HT 13.4%		
	(France) range (6–34%)		

Reference [29].

Table 4: 8 years results of conservative and radical treatments in 716 DCIS.

	MX (145)	CS (136)	CS + RT (435)
Type of surgery	20.25%	18.09%	60.75%
8-year local recurrence rate	2.1% (3)	30.1% (41)	13.8% (60)
Noninvasive local recurrence	0% (0)	41.46% (17)	40% (24)
Invasive local recurrence	100% (3)	58.53% (24)	60.0% (36)
Nodal recurrence	0	3.7%	1.8%
Metastases	1.4% (2)	4.4% (6)	1.4% (6)
(All distant metastases occurred after previous invasive LR)			
Metastases among cases of invasive LR in CS and CS + RT 19% (12/60)			

Reference [32].

overlying skin), skin-sparing approach (SMM), and, most recently, nipple-preserving techniques. In addition MX for DCIS is particularly suited to immediate breast reconstruction with an implant or autologous flap, as adjuvant RT and axillary involvement are less likely. The preservation of the natural skin envelope and inframammary fold during skin-sparing mastectomy would seem an ideal option to improve the aesthetic outcome of the instant reconstructive time, provided that clear margins are achieved. There has been a concern that it compromises the completeness of a mastectomy resulting in an increase in local breast cancer recurrence but large studies concluded that SSM or DCIS was an oncologically safe procedure with an LR rate similar to conventional MX (1–3%) [34].

The original Van Nuys prognostic index was created by combining lesion parameters and local recurrence as the markers of treatment failure. In the attempt to quantify the known important prognostic factors in DCIS, the USC/VNPI is offered as a guideline in a scientifically based discussion with the patient in order to define appropriate treatment. In Silverstein, patients with USC/VNPI scores of 10, 11, or 12 showed the greatest absolute benefit from postexcisional radiation therapy, but their LR rate continues to be extremely high and a recommendation for mastectomy should be considered [25]. In the future other factors like molecular markers may be integrated into the index to the extent that they are shown to be statistically important predictors of local relapse.

3.3. Breast Conserving Surgery. In spite of its often larger size, DCIS is a local disease lacking of two important components of the fully expressed malignant phenotype like stromal invasion and distant metastases. Its distribution is almost always segmental (unicentric) and complete excision is theoretically possible to achieve local clearance [24].

Faverly et al. have attributed the reliability of histological margin assessment to proliferation type, showing that continuous and multifocal growth pattern are usual in poorly and well differentiated in situ, respectively. However, in this series, only 8% of DCIS in 60 mastectomy specimens have a multifocal distribution with gaps greater than 10 mm, and this theoretically low likelihood of false free margin should encourage the use of conserving treatment for eradicable tumors [35].

Available data suggest that local control is optimized by the lumpectomy adequacy, regardless of the number of re-excisions required to achieve margin-negative status [36, 37]. Several investigators have also demonstrated that a diagnostic needle biopsy is associated with a higher success rate for subsequent BCS, improving single lumpectomy procedure results. The surgeon will plan a therapeutic partial breast resection with a more aggressive approach when the aim is to achieve margin control compared with when the goal is to sample adequately for a tissue diagnosis [38]. However, controversy remains regarding the oncological adequacy of BCS alone and the variable local relapse risk in randomized clinical trials evaluating DCIS treatment. In the National Surgical Adjuvant Breast Project (NASBP B-17) the overall recurrence rate for patients treated with excision only was 32% at 12 years, and 16% for patients treated with excision plus irradiation. At 4 years of follow-up, 9% of patients treated with excision plus radiation therapy had a local recurrence compared with 16% of DCIS treated with excision only in the EORT results, showing a statistically significant (approximately 50%) reduction in LR for patients who received RT [30].

Optimal local control is essential because in most reported series, approximately half of all local recurrences are invasive in each treatment group. In fact, breast preservation, with or without RT, yields a better cosmetic results but is accompanied by an increase in the probability of local failure.

The clinical value of recurrent DCIS is different from primary lesions and the prognostic implications of invasive disease are significant.

In particular the overall risk of metastasis has been reported to 0–3.6% for in situ LR, compared to 13.2–18% after invasive LR, and the axillary lymph node involvement with invasive LR is estimated from 11 to 30% [39, 40]. In Silverstein series the 8-year breast cancer-specific mortality and distant disease probability for 74 patients with LR previously treated for DCIS were 8.8% and 20.8%, respectively, while for the 35 invasive recurrences subgroup they were 14.4% and 27.1% [41].

Multivariate analysis showed that margin width, age, nuclear grade, and tumor size were all independent predictors of local recurrence ($P < .001$), with margin width as the single most important variable [42].

In 445 patients dataset with pure DCIS treated with excision alone, Heather at al. described the incremental benefit of larger margins. The median tumor size was 10 mm and after a median follow-up period of 57 months only 9 of 197 (4.6%) patients with a greater than 10 mm margin experienced local failure (Table 5). The probability of remaining free of local recurrences at 5 years was 93% without postoperative radiotherapy. The relative risk of developing an LR stratified by surgical margins was plotted as a continuous variable with a clear trend on decreasing the hazard ratio for local failure [43].

According to this approach, the most likely cause of local recurrence after excision alone for DCIS is inadequate surgery resulting in residual disease. In a previously reported data from 181 intraductal breast carcinoma, 76% of patients with initially involved margins had residual DCIS at mastectomy or reexcision, as did 43% of patients with initially clear margin (>1 mm) [44].

Neuschatz et al. analyzed reexcision specimens of 253 patients treated with lumpectomy for DCIS identifying residual disease in 63% of patients with transected margins, compared to 41% with greater than 0 to 1 mm, and to 31% with greater than 1 to 2 mm margins (Table 6) [17].

Yet one of the most important questions in the complex decision-making progress regards which patients selected for breast preservation require postexcisional radiation therapy. In our opinion, exploring the prognostic implications of histopathological features in BCS should be an excellent predictor of outcome, and with further corroboration, margin, width alone could possibly be used to determine the need for adjuvant RT in different risk subgroups.

The survival curves from the Van Nuys series showed that, regardless of the presence of high nuclear grade, comedonecrosis, large tumor size, or young age, the risk of local relapse remains slight if wide margins of resection are achieved. Consistent with the NSABP B-17 and EORTC trial findings, the absolute reduction of LR by RT increased with time from 7% at 4 years to 11% at 10.5 years but successive studies recognized that postoperative RT may not significantly improve the local outcome in all types of DCIS [27].

Di Saverio et al. confirmed the variable benefits of adding RT for different subsets of patients and so questioning the suitability of a uniform treatment policy. There was no advantage in the low VNPI score subgroup while it should be noted that in the groups with the higher VNPI score the benefit from adjuvant RT in avoiding local recurrence could be greater. Disease-Free Survival (DFS) at 10 years was 94.7% in CS compared to 92.3% in CS + RT in low VNPI (4-5-6) score group, 78.5% and 86.8% in the intermediate VNPI (5-6-7), and 50% against 100%, respectively, in the high VNPI (10-11-12) [31].

In the evaluation of USC/VNPI, Melvin et al. focused on the impact of margin status score on local recurrence. With margins 1–9 mm (score 2), there was a significant trend toward a benefit from irradiation. With margins less than 1 mm (score 3), there was a highly significant decrease in the probability of LR if radiation therapy was added [24].

These data suggest that margin width should be valued as an excellent predictor of local recurrence probability, and consequently, of the likelihood of residual DCIS. Silverstein et al. reported an 8% local recurrence rate for all conservatively treated DCIS lesions with margins of 10 mm or greater (VNPI score 1) [45] and Lagios and Silverstein showed a 5% local recurrence rate for all conservatively treated patients with the same margin status and lumpectomy alone compared to 4.5% in those treated by lumpectomy and irradiation [46].

In the selection process of pure DCIS cases, Van Nuys Prognostic system can be applied in conjunction with clinical experience to study tumor morphology and detection rate of local recurrence as the primary end points. Radiation therapy is not without side effects changing the texture of the breast and making subsequent mammography more difficult to interpret. Furthermore, its use may preclude the chance to implement a conservative treatment should it be needed in the future [47].

Consequently, subsets of patients who are not likely to receive any significant benefit from radiation therapy can be identified.

DCIS cases with VNPI scores of 3 or 4, low-grade lesions, small noncomedo lesions with uninvolved margins or well-differentiated lesions can be considered for treatment with excision only. This can be an important therapeutic cornerstone since such patients may account for more than 30% of the total number [48].

Patients with intermediate scores (5, 6, or 7) received a statistically significant 17% LR-free survival benefit when treated with radiation therapy ($P = 0.017$) but treatment recommendations for the intermediate group are the most difficult. DCIS cases with scores of 8 or 9, although showing the greatest relative benefit from RT, experienced LR rate in excess of 60% at 8 years and should be considered for mastectomy, generally with immediate reconstruction or reexcision if technically possible [41].

This controversy over the treatment selection may lead to a new conceptual approach on the operational chance of

Table 5: Breast conservative surgery (BCS) results without RT.

Authors	Patients	Margin width	Local recurrence	Follow-up
Fischer et al. (2001) [58]	818	1 mm	31%	10 years
BiJker et al. (2001) [59]	1010	3 mm	13%	10 years
Houghtons et al. (2003) [60]	1701	1 mm	22%	4 years
Warren et al. (2005) [61]	1103		15%	7 years
Sabin et al. (2011) [62]	670	3 mm	High grade 18% Low grade 10.5%	7 years
Heather et al. (2005) [43] (median tumor size 10 mm)	197	>10 mm	4.6%	5 years

Table 6: Reexcision specimens analysis in patients treated with lumpectomy for DCIS.

	Margin Width (mm)	Residual Disease
(i) Silverstein et al. [44]	≥1 mm	43%
	<1 mm	76%
(ii) Neuschatz et al. [17]	0 mm (transected)	63%
	0-1 mm	41%
	1-2 mm	31%

surgically modifying VNPI score and thus influencing the choice of more or less invasive strategy.

Potentially, in some cases, a patient can choose a reexcision, in order to downscore her lesion where the safety predictive criteria cannot be guaranteed. Successful downscoring of a patient with a USC/VNPI or 10 or 11 could result in substantial reduction in the risk of local recurrence, perhaps changing a recommendation from mastectomy to radiation therapy. Similarly, patients with close or involved margins with USC/VNPI scores of 7 or 8 after initial excision could opt for reexcision and a successful downscoring by achieving widely clear margins. This could result in a final score sufficiently low to avoid breast irradiation.

Moreover a dynamic surgical technique may be the basis for consolidating the diagnostic paradigms and further decrease the downtreatment risk.

In some case, reexcision will upscore the tumor, increasing the USC/VNPI by revealing a larger tumor size, a higher nuclear grade, the presence of previously undetected comedo necrosis, or an involved margin, suggesting in this way that mastectomy is preferable to select [25].

We deem prudent that the choice is acquired together, having surgeon to assist the patient to achieve his more or less conservative goal, according to the subjective and variable security needs and by counseling in a rational manner.

Moreover, due to the molecular heterogeneity of DCIS as well as the increasing trend toward individualized cancer treatment [49, 50], a Nomogram for predicting the risk of local recurrence after breast-conserving surgery published by Rudloff et al. integrates ten clinicopathologic variables to provide the probability of LR at 5 and 10 years after BCS. The risk estimate is specific on the individual patient and the final regression model was chosen according to the clinical and statistical significance of categorical variables like age at the time of surgery, family history, initial presentation, radiation therapy, adjuvant endocrine therapy, nuclear grade, necrosis, margins, number of excisions, time period of surgery, and their interdependent relationships. This tool may assist in individual decision making regarding various surgical or treatment options and help avoid over- and undertreatment of noninvasive breast cancer showing it to have favorable predictive accuracy and good model calibration [51].

Furthermore, we think that a more invasive procedure can be oriented on the axillary side as selective sentinel lymph node biopsy (SLNB) whose diagnostic mode has less aesthetic responsibility but a great role on therapy selection process.

In retrospective analysis of diagnostic procedures the invasion underestimation in needle biopsies of DCIS and the improvement in the sentinel practice have led some authors to support the lymphatic mapping at the surgery time [52]. In Lee et al. study there was no association between age, nuclear grade, tumor size, or presence of a mass in determining the likelihood of invasion, and of 59 patients diagnosed with DCIS by stereotactic biopsy, 29% were subsequently found to have invasive disease after surgery [53].

The status of the axillary lymph nodes remains the most powerful prognostic indicator of invasive breast cancer, but the role of axillary staging with SLNB for DCIS is controversial [54]. Nonetheless, surgeons have been removing lymph nodes in patients with a primary diagnosis of DCIS for a variety of reasons and with variable results [55]. This is consistent with findings from the recent French survey which reported overall rates of 21.3% for SLNB and 10.4% for axillary dissection (AD) [29]. Positive sentinel nodes have been reported in 0% to 13% of DCIS patients but among published studies, the incidence of SLNB metastasis among patients with initial diagnosis is substantially higher than among those with a final diagnosis like after excision or mastectomy (9.8% versus 5.0%) [3]. The information

from axillary dissection or SLNB was of little value in the treatment of patients in whom no invasive cancer was found but it remains an attractive option when considering DCIS. The absolute indication for SLNB remains histological confirmation of concurrent or recurrent invasive disease. Therefore, in patients diagnosed with DCIS on core biopsy examinations SLNB should be reserved for those at high risk of invasive disease, including patients with palpable lesions, DCIS larger than 40 mm, high nuclear grade, comedo morphology, necrosis or recurrent disease, or patients undergoing mastectomy where SLNB could not be postponed [55].

Moreover axillary node involvement is higher with DCISM (5.1%) than that with DCIS (1.4%) and inadequate sampling could result in misdiagnosis and consequent under-treatment of patients [5]. The incidence rate of microinvasion among all DCIS cases is approximately 14% [56], and this theoretical foundation can support the significance of stratification risk in the practice of nodal spread staging procedure, in order to change the prognosis.

4. Conclusion

Since our knowledge of ductal carcinoma in situ (DCIS) continues to evolve, treatment decisionmaking has become increasingly complex and controversial for both patients and physicians. It represents a broad biologic spectrum of disease with a wide range of molecular heterogeneity, treatment approaches, and clinical recommendations but the need of local control should guide our decisions regarding therapy and help to risk stratify patients.

It is often difficult to justify mastectomy during an era of increasing practice of conservation for the more aggressive lesion (invasive breast cancer), but not all patients are candidates. The other side is to understand and define more accurately the application range of conservative treatment and its dynamic potential. Target is to treat patients effectively and decrease the risk of local recurrence, selecting the approach that will significantly benefit each patients group and not subject them to unnecessary risk. Specifically, the sophisticated questions that patients and doctors ask today are which subgroups of DCIS will benefit from postexcisional radiation therapy and how much and which can be treated by excision alone. Certainly the gold standard in clinical practice must be designed with an integrated approach to diagnostic and therapeutic features and functional skills aggregation. Nomograms are graphical depictions of predictive models that provide overall probability of a specific outcome for an individual patient, and in consultation with a physician, these tools can be used by patients to make decisions regarding various treatment options. The objective is to overcome the conflict between extent of resection, need of adjuvant strategies, and final aesthetic result with good oncological radicality.

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Clinical Study

The Role of Preoperative Bilateral Breast Magnetic Resonance Imaging in Patient Selection for Partial Breast Irradiation in Ductal Carcinoma *In Situ*

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Purpose. Women with ductal carcinoma *in situ* (DCIS) are often candidates for breast-conserving therapy, and one option for radiation treatment is partial breast irradiation (PBI). This study evaluates the use of preoperative breast magnetic resonance imaging (MRI) for PBI selection in DCIS patients. *Methods*. Between 2002 and 2009, 136 women with newly diagnosed DCIS underwent a preoperative bilateral breast MRI at Mayo Clinic in Florida. One hundred seventeen women were deemed eligible for PBI by the NSABP B-39 (National Surgical Adjuvant Breast and Bowel Project, Protocol B-39) inclusion criteria using physical examination, mammogram, and/or ultrasound. MRIs were reviewed for their impact on patient eligibility, and findings were pathologically confirmed. *Results*. Of the 117 patients, 23 (20%) were found ineligible because of pathologically proven MRI findings. MRI detected additional ipsilateral breast cancer in 21 (18%) patients. Of these women, 15 (13%) had more extensive disease than originally noted before MRI, and 6 (5%) had multicentric disease in the ipsilateral breast. In addition, contralateral breast cancer was detected in 4 (4%). *Conclusions*. Preoperative breast MRI altered the PBI recommendations for 20% of women. Bilateral breast MRI should be an integral part of the preoperative evaluation of all patients with DCIS being considered for PBI.

1. Introduction

Ductal carcinoma *in situ* (DCIS) is a noninvasive breast cancer and represents a complex pathologic condition in which malignant epithelial cells arise and proliferate within the ducts of the breast but do not invade the basement membrane. According to the Surveillance Epidemiology and End Results program (SEER), DCIS represents 14% of all new breast cancer diagnoses in the United States [1].

Radiation therapy has historically been delivered to the whole-breast after breast-conserving surgery. Adjuvant radiation has been shown to improve local tumor control in multiple prospective, randomized clinical trials [2–4]. Partial breast irradiation (PBI) has been developed as a way to deliver radiation directly to the tumor cavity of the breast after breast-conserving surgery in lieu of whole-breast radiation therapy. PBI can be delivered by multiple techniques, including interstitial and intracavitary brachytherapy, intraoperative radiotherapy, 3-dimensional (3D) conformal or intensity-modulated radiation therapy, or proton therapy. As less breast tissue is being irradiated, the potential benefits include decreased acute toxicity to the breast and potential decreased risk of late toxicity due to reduced radiation dose to the surrounding tissue [5]. This reduced risk includes the potential for decreased heart and lung toxicity [6]. An additional benefit to patients is the decreased total

treatment time. One commonly used course of PBI is 34 gray administered twice daily over 5 days, for a total of 10 fractions. Multiple fractionation schemes have been used, including single-fraction treatments. For a select group of patients, equivalent results have been reported for PBI versus whole breast external beam radiotherapy [5, 7, 8].

The National Surgical Adjuvant Breast and Bowel Project, Protocol B-39 (NSABP B-39) is a prospective randomized trial in which eligible women with early-stage breast cancer are randomized to whole-breast radiation therapy versus PBI. Specific eligibility criteria include tumor size ≤3 cm, ≤3 positive lymph nodes, negative surgical margins, lack of multicentric disease, and no contralateral breast cancer.

Bilateral breast magnetic resonance imaging (MRI) is being used preoperatively with increasing frequency for women with a new diagnosis of breast cancer. MRI has been found to enhance findings in women when performed after an initial clinical evaluation. Specifically in DCIS, MRI has been prospectively shown to have a sensitivity of 92%, and up to 98% for high-grade DCIS [9]. Multiple meta-analyses, which include DCIS patients, have shown that MRI of the ipsilateral breast detects additional disease in 16–20% of women with newly diagnosed breast cancer [10, 11]. After an initially negative evaluation, contralateral breast cancer is detected by MRI in 3% to 6% of patients [11, 12]. These results have been shown to alter surgical recommendations [10–12].

This study evaluates the role of bilateral breast MRI in determining eligibility for PBI based on the NSABP-B39 criteria in women with newly diagnosed DCIS.

2. Methods

This is a retrospective review of women diagnosed with DCIS at Mayo Clinic in Florida between 2002 to 2009. All women with a new diagnosis of DCIS who underwent a preoperative bilateral breast MRI, regardless of their ultimate treatment, were included in this study. Data collected on these women included patient demographics, tumor characteristics, MRI findings, and pathologic information. At Mayo Clinic in Florida a preoperative bilateral breast MRI is recommended as part of the evaluation of all women with a new diagnosis of DCIS.

Women with DCIS were initially evaluated after the standard clinical evaluation, which consisted of physical examination, mammogram and/or ultrasound, and pathologic examination of a tissue biopsy. On the basis of the initial clinical evaluation, each patient was determined to be eligible or ineligible for PBI according to the NSABP B-39 criteria. These criteria included tumor size ≤3 cm (including multifocal tumors to a maximum extent of 3 cm); negative final surgical margins; lack of multicentric disease; no contralateral breast cancer. Multicentric disease was defined as additional disease >4 cm from the original tumor volume or disease within a different breast quadrant. Negative surgical margins are defined as histologically free of invasive and noninvasive tumor. Each patient was reviewed again after the bilateral breast MRI, and the eligibility for PBI was reassessed. All changes in PBI recommendations made on the basis of MRI findings were confirmed by final pathology. Tumor specimens were histologically evaluated, and final DCIS tumor size was determined by the maximum histologic size. Patients were excluded from analysis if any of these criteria were not met.

Breast MRI examinations were performed with the patient in the prone position in a 1.5-tesla system (Avanto, Espree, Sonata, or Symphony; Siemens Medical Solutions USA Inc., Malvern, PA), using a dedicated surface breast coil. The imaging sequence included an axial pre-contrast 3D fast low-angle shot (FLASH) sequence, T1-weighted, 3D, gradient-echo scans of both breasts, followed by a sagittal T2-weighted turbo spin echo sequence of each breast. Slice thickness was 3 mm with a 0.6 mm gap for all images. The next series of images obtained included sagittal 3D flash images of the breast with known cancer, then imaging of the contralateral breast using the same technique, both before and after a bolus of intravenous gadodiamide (Omniscan; GE Healthcare, Waukesha, WI). If the patient's glomerular filtration rate was higher than 60 mL/min, 20 mL of gadobenate dimeglumine (MultiHance; Bracco Diagnostics Inc,, Princeton, NJ) was used, and if the glomerular filtration rate was 30 to 60 mL/min, 15 mL of gadobenate dimeglumine was administered. Patients with a glomerular filtration rate <30 mL/min were not given a contrast agent unless it was deemed absolutely necessary. Finally, bilateral axial postcontrast 3D FLASH images were obtained using the above-described parameters. Postprocessing included subtraction of the pre- and postcontrast images and motion correction, if necessary. MRIs were interpreted by board-certified, subspecialist breast radiologists.

Patients who were deemed ineligible for PBI on the basis of their bilateral breast MRI were categorized by the reasons for their ineligibility. Specifically, women were ineligible if the size of the tumor was described on MRI (and pathologically proven) to be >3 cm. Also ineligible were patients with multifocal disease if the total tumor extent was >3 cm. These patients were classified as having more extensive disease than determined by initial clinical evaluation. Patients were also deemed ineligible if they were diagnosed with multicentric breast cancer, which was defined as additional disease >4 cm from the original tumor volume or disease within a different quadrant. If any cancer diagnosis was made in the contralateral breast, the patient also was deemed ineligible. Results were confirmed postsurgically with the final pathologic findings.

3. Statistics

Characteristics of patients, final pathology results, and MRI findings were summarized by sample median, 25th percentile and 75th percentile for numerical variables, and by number and percentage for categorical variables. For evaluation of the primary aim, the proportion of DCIS patients whose eligibility for PBI was altered by bilateral breast MRI findings was estimated along with an exact binomial 95% confidence interval (CI). All analyses were performed using SAS (version 9.2; SAS Institute Inc., Cary, NC).

Table 1: Characteristics of 117 women with DCIS eligible for partial breast irradiation on the basis of an initial clinical evaluation, and of the 23 women ultimately ineligible by MRI.

Variable	Overall ($N = 117$)	Ineligible based on MRI findings ($N = 23$)
	No. (%)[a]	
Age at diagnosis, y		
31–40	3 (3%)	1 (4%)
41–50	20 (17%)	4 (17%)
51–60	31 (26%)	4 (17%)
61–70	25 (21%)	4 (17%)
71–80	30 (26%)	7 (30%)
81–91	8 (7%)	3 (13%)
Race		
African American/Black	4 (3%)	1 (4%)
Asian	1 (1%)	0 (0%)
Caucasian	105 (90%)	21 (91%)
Hispanic	4 (3%)	1 (4%)
Other	3 (3%)	0 (0%)
Menopausal status		
Post	89 (76%)	16 (70%)
Pre	28 (24%)	7 (30%)
No. of first degree relatives with history of breast cancer		
0	85 (73%)	14 (61%)
1	23 (20%)	6 (26%)
2-3	8 (7%)	2 (9%)
Unknown/not available	1 (1%)	1 (4%)
No. of relatives with history of breast cancer		
0	71 (61%)	13 (57%)
1	27 (23%)	5 (22%)
2–4	18 (15%)	4 (17%)
Unknown/Not available	1 (1%)	1 (4%)
Dense breasts		
No	32 (27%)	8 (35%)
Yes	79 (68%)	14 (61%)
Not reported/indeterminate	6 (5%)	1 (4%)
Detection method		
Mammogram	105 (90%)	19 (83%)
Palpation	10 (9%)	3 (13%)
Other	2 (2%)	1 (4%)
Lumpectomy	68 (58%)	4 (17%)
No. of days from diagnosis to MRI	14 (0, 9, 23, 95)	12 (4, 8, 22, 34)
No. of days from diagnosis to surgery	38 (6, 27, 56, 813)	36 (21, 27, 57, 813)

[a] Sample median (minimum, 1st quartile, 3rd quartile, maximum) is given for numerical variables, whereas *n* (%) is given for categorical variables.

4. Results

Between January 2002 and June 2009, 136 women with newly diagnosed DCIS underwent a preoperative bilateral breast MRI. Of these patients, 117 women (86%) were deemed eligible for PBI based on the NSABP-B39 inclusion criteria after their initial clinical evaluation (i.e., a physical examination, mammogram and/or ultrasound, and pathologic findings). Characteristics of the 117 women (median age, 63; range 36–90) who were initially eligible for PBI are summarized in Table 1.

The pathologic results of the women who were recommended to undergo a biopsy following MRI were evaluated. In this cohort, 39% of women were recommended to have

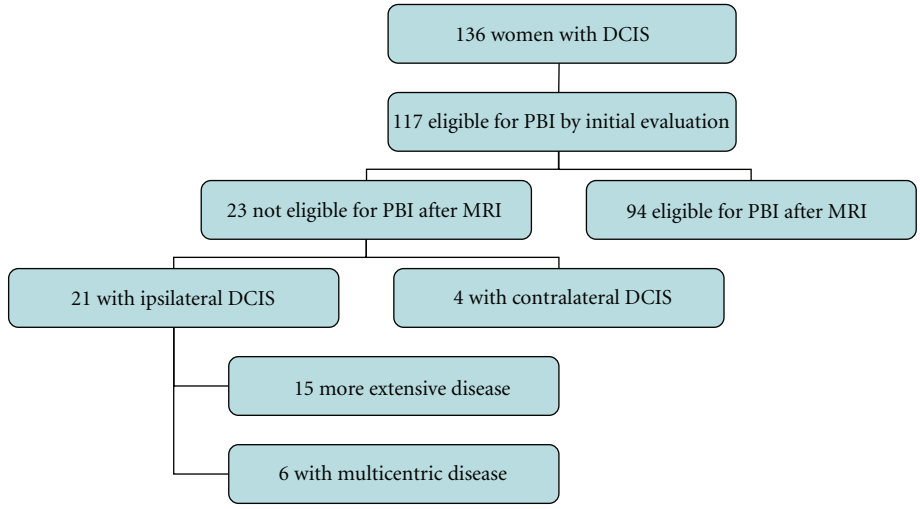

Figure 1

a biopsy either of the ipsilateral, contralateral, or bilateral breasts. Of these patients, 37% were found to have additional cancer.

MRI findings led to pathologically proven additional disease that altered the recommendations for PBI in 23 (20%; 95% CI: 13%–28%) of the 117 patients initially eligible for PBI. MRI detected additional ipsilateral breast cancer in 21 (18%) patients. Of these women, 6 (5%) were diagnosed with multicentric breast cancer. A total of 15 (13%) women became ineligible for PBI due to more extensive disease as determined by MRI and confirmed by pathologic results. Contralateral breast cancer was detected in 4 (4%) women on the basis of MRI results (Figure 1). Two women were found to have both additional ipsilateral disease and contralateral breast cancer.

Table 2 summarizes the final pathologic findings of the 117 women initially deemed appropriate for PBI, and of the 23 women ultimately ineligible for PBI. Within this group, 8 (7%) patients were ultimately diagnosed with invasive breast cancer.

A total of 15 patients had more extensive disease and the median tumor size in this group was 4.0 cm. Of the 6 patients with multicentric disease, all additional tumors were smaller than 1 cm, and none of the patients had more than 2 tumors. The 4 patients with contralateral tumors detected by MRI were all smaller than 2 cm.

5. Discussion

This study evaluates the use of bilateral breast MRI as a diagnostic tool for women with newly diagnosed DCIS being considered for PBI following breast conserving surgery. Of 117 patients deemed eligible for PBI after their initial clinical evaluation, 20% became ineligible after MRI. Reasons for ineligibility included additional findings of more extensive disease, multicentric breast cancer, or contralateral breast cancer.

Previous studies have focused on invasive cancers exclusively, or in combination with non-invasive cancers. This is the first published study evaluating the role of MRI in determining patient eligibility for PBI exclusively in patients with DCIS. Previous studies, including our unpublished data, show a change of 2–11% in PBI recommendations for all breast cancer patients with a diagnosis of multicentric disease after breast MRI [13–18]. Multifocality has also been evaluated with a range of 4–7% change in PBI recommendations. Contralateral breast cancer diagnoses after MRI have produced a 2–5% change in PBI recommendations [13–18].

This study found 5% of patients had a change in PBI recommendations after MRI because of additional findings of multicentric disease. This correlates with the published data, as does the 4% change in PBI recommendations after MRI for contralateral disease. This study did not examine only multifocal disease, but it did evaluate multifocal disease that led to ineligibility, as well as disease larger on MRI and confirmed by pathology, which was defined as more extensive disease. Therefore, the percentage of patients with altered treatment recommendations because of more extensive disease (13%) was greater than that in published reports from previous studies that evaluated multifocal disease alone.

These results for DCIS correlate well with those reported in the medical literature on additional diagnoses made by MRI. About one-fifth (18% (21/117) of the patients had altered eligibility either because of multicentric disease, multifocal disease, or larger disease within the ipsilateral breast, which correlates well with the 16–20% additional ipsilateral breast cancer diagnoses reported in the MRI literature [10, 11]. The 4% of patients in whom a contralateral breast cancer was diagnosed also correlates well [11, 12]. It is important to note that of the 20% of patients ineligible for PBI, not all of these women would have been excluded from consideration of breast-conserving surgery.

All the patients included in this study underwent an MRI on a 1.5-T machine. Plana et al. found a statistically significant higher positive predictive value for breast

Table 2: Final pathological results for 117 women eligible for partial breast irradiation on the basis of the initial clinical evaluation, and of the 23 women ultimately ineligible by MRI.

Variable	Overall ($N = 117$)	Ineligible based on MRI findings ($N = 23$)
	No. (%)[a]	
Tumor size (cm)		
Not available	8 (7%)	0 (0%)
0.1-1.0	61 (52%)	6 (26%)
1.1–2.0	28 (24%)	3 (13%)
2.1–3.0	9 (8%)	3 (13%)
>3.0	11 (9%)	11 (48%)
Number of tumors (>1)	14 (12%)	8 (35%)
EIC (positive)	6 (5%)	4 (17%)
T stage		
Tis	109 (93%)	18 (78%)
T1a	6 (5%)	3 (13%)
T1b	1 (1%)	1 (4%)
T2	1 (1%)	1 (4%)
N stage		
NX	44 (38%)	5 (22%)
N0	70 (60%)	16 (70%)
N1	3 (3%)	2 (9%)
Lymphovascular space invasion		
No	113 (97%)	23 (100%)
Yes	1 (1%)	0 (0%)
Not reported/indeterminate	3 (3%)	0 (0%)
Lobular features	1 (1%)	1 (4%)
Grade		
Low	26 (22%)	10 (43%)
Intermediate	25 (21%)	2 (9%)
High	66 (56%)	11 (48%)
ER		
Negative	25 (21%)	8 (35%)
Positive	89 (76%)	14 (61%)
Not tested/not available	3 (3%)	1 (4%)
PR		
Negative	36 (31%)	10 (43%)
Positive	77 (66%)	12 (52%)
Not tested/not available	4 (3%)	1 (4%)

EIC: extensive intraductal component. ER: estrogen receptor. PR: progestin receptor.
[a]Values are numbers (percentage).

MRI when using ≥1.5 T MRI [11]. MRI has also been found to have a high sensitivity for DCIS as reported by Kuhl et al. with 1.5T machines [9]. Some previous studies used 1-T MRI, which may have led to decreased detection of additional disease.

This study is limited as a retrospective review. It is, however, the first study conducted to date that evaluates the role of MRI in determining appropriate candidacy for PBI for women with DCIS. It is also a more thorough evaluation about the utility of MRI for not only evaluating multicentric and contralateral breast cancers but also for evaluating more extensive disease, including tumors >3 cm and multifocal disease that extends >3 cm within the breast. By including more extensive disease, an additional 13% of women were identified as being ineligible for PBI after breast MRI than by evaluation of multicentricity and contralateral disease alone.

6. Conclusions

These results show that 20% of women with DCIS became ineligible for PBI after a bilateral breast MRI. Recognition

of PBI ineligibility prior to surgery can improve clinical planning, including the avoidance of unnecessary procedures associated with brachytherapy and intraoperative radiation therapy. Bilateral breast MRI should be an integral part of the preoperative evaluation of all patients with DCIS who are being considered for PBI.

Conflict of Interests

The author declare that there is no conflict of interests.

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Review Article

Radiotherapy after Conservative Surgery in Ductal Carcinoma In Situ of the Breast: A Review

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Several large prospective and retrospective studies have demonstrated excellent long-term outcomes after breast conservative treatment with radiation in invasive breast cancer. Breast-conserving surgery (BCS) followed by radiotherapy (RT) is an accepted management strategy for patients with DCIS. Adding radiation treatment after conservative surgery enables to reduce, without any significant risks, the rate of local recurrence (LR) by approximately 50% in retrospective and randomized clinical trials. As about 50% of LRs are invasive and have a negative psychological impact, minimizing recurrence is important. Local and local-regional recurrences after initial breast conservation treatment with radiation can be salvaged with high rates of survival and freedom from distant metastases.

1. Introduction

The term ductal carcinoma in situ (DCIS) encompasses a heterogeneous group of lesions with different biological potential and clinical behaviour [1].

There is no consensus regarding how to optimize the treatment for patients with DCIS: mastectomy cures almost all patients, but it is considered an overtreatment in many cases, particularly when they are small mammographic-detected lesions.

Most women are eligible for breast conservative surgery (BCS), a major decision is whether or not radiotherapy (RT) must follow surgical excision in order to control any microscopic residual disease. It is likely that not all patients with DCIS require RT following BCS; it is important to identify patients at high risk of recurrence or progression to invasive breast cancer who can benefit from RT. It is argued that RT should be used selectively, because of possible short- and long-term morbidity, and also because radiation fibrosis may hamper interpretation of follow-up mammograms.

Unfortunately, until now, the ability to select DCIS that is likely to recur or progress to invasive breast cancer is still limited, and there is a lack of level-1 evidence supporting the omission of adjuvant RT in selected low-risk cases, which could potentially be adequately treated by complete local excision.

Patients with DCIS treated with BCS may recur approximately in the same proportion either as DCIS or invasive breast cancer [2]. Efforts have continued to attempt to define the subsets of patients to whom we should offer the different treatment options for local treatment (surgical excision alone or plus radiation or mastectomy). Most of the DCIS patients are interested in breast conservative treatment and consequently a major decision is whether or not to add radiation treatment. Irrespective of whether a low-risk group can be identified, the role of radiation after wide excision of DCIS remains controversial.

The aim of this paper is to report and summarize the indications for RT after BCS and the results of retrospective, prospective randomized studies and meta-analyses on this issue.

2. Retrospective Studies

Published population-based retrospective mono-institutional and collaborative studies have demonstrated excellent long-term outcomes after BCS with RT.

Multiple observational studies report lower rates of recurrence (DCIS or invasive) for patients undergoing BCS + RT over BCS alone. All but one [3] of the observational studies show a lack of mortality benefit associated with BCS + RT compared with BCS alone.

Surveillance, Epidemiology, and End Results data have shown that still a substantial number of patients in the United States are treated with excision alone, without radiation [4].

An international collaborative multi-institutional study conducted by 10 Institutions in Europe and North America involving 1003 patients with mammographically detected DCIS has been published with long-term results [5]. Adjuvant tamoxifen was not used. The median followup was 8.5 years; the 15-year overall survival (OS) was 89%, and the 15-year cause-specific survival (CSS) was 98%.

The rate of any local recurrence (LR) (DCIS plus invasive) was 19%. Significant factors for LR were found to be the final pathologically positive margins and the patient's younger age. For the favorable subgroup of patients aged ≥50 years with negative margins, the 10-year rate of local failure was ≤8%.

A retrospective French collaborative study reported on 882 DCIS treated from 1985 to 1995 [6]. Mastectomy, BCS alone, and BCS + RT were performed, respectively, in 20%, 22%, and 58% of patients. Thus 515 women out of 705, who were treated with BCS, received adjuvant RT; a 10 Gy boost was given to 52% of them. Hormonal therapy was administered to 13.4% of the patients. The crude 7-year LR rate was 2% (mastectomy subgroup), 31% (BCS subgroup), and 13% (BCS + RT subgroup) ($P < 0.0001$). RT reduced the LR rate by 65% in all histological subgroups, especially in comedocarcinoma and mixed cribriform/papillary subgroups.

The most numerous single institution series was published by the William Beaumont Hospital (USA) in 2005 [7]. Between 1981 and 1999, 410 cases were treated; 367 were managed with BCS (54 with lumpectomy alone and 313 with adjuvant RT—median dose: 45 Gy). Of these 313 patients, 298 received also a boost with a median dose of 16 Gy. Thirty patients (8.2%) experienced an ipsilateral breast tumor recurrence after breast conservative treatment; 25/313 patients (8%) after RT, 5/54 (9.3%) after BCS alone, and 2/43 (4.7%) developed a chest wall recurrence after mastectomy. Ten-year rates of LR, CSS, and OS were similar after mastectomy and breast conservative treatment. Young age (<45 years), close/positive margins, no breast irradiation, and lower electron boost energies (≤9 MeV) were associated with a higher risk of LR.

Schouten van der Velden et al. [8] published the results of a multicenter dutch retrospective study on 798 women treated between 1989 and 2003, selected by the Tumor Registry of the Comprehensive Cancer Centre East Netherland. The 5-year recurrence-free survival (RFS) was 75% for BCS alone (237 patients) compared to 91% for BCS followed by RT (153 patients) and 99% for mastectomy (408 patients) ($P < 0.01$). Independent risk factors for LR were treatment strategy, symptomatically detected DCIS, and presence of comedo necrosis. Margin status reached statistical significance only for patients treated with BCS.

A very large retrospective experience is reported by the Van Nuys group [9]. Nine hundred and nine cases were reported, treated from 1971 to 2000; 326 of them underwent mastectomy, 237 BCS + RT, and 346 BCS alone. In the group of patients treated conservatively (583), the LR rate was 28% after BCS alone and 20% after BCS + RT ($P = 0.06$), with a median time to LR of 25 and 57 months, respectively ($P < 0.01$). It has to be noted that in the RT group there were more patients with "close" (<1 mm) margins (35% versus 19%), and the median followup was 36 months longer. After having observed the importance of several factors (grading and comedo necrosis, size, and margins), Silverstein et al. proposed the well-known Van Nuys Prognostic Index (VNPI) [10] based on a three-point score for each predictor. In 2003, they added age to their prognostic score [11], identifying three risk subgroups: ≤39 years of age (high score), 40–60 years of age (intermediate score), and ≥61 years of age (low score). To patients with a low score (from 4 to 6), conservative surgery alone was recommended, to those with an intermediate score (from 7 to 9) postsurgical RT, and to those with a high score (from 10 to 12) mastectomy, since the LR incidence at 5 years appeared too high (around 50%) with a BCS + RT treatment.

Although a simple, and apparently easy task, this score, based on retrospective analysis of Van Nuys case studies, has not been easily reproduced in clinical practice and has not been still validated in a prospective study [12, 13].

Another collaborative group in Italy published the data of 139 cases of DCIS treated with BCS + RT, with a median followup of 81 months [14]. Actuarial OS, CSS, and RFS at 10 years were 93%, 100%, and 86%. The same group reported on 112 cases of subclinical DCIS treated between 1982 and 1993 [15]. At a median followup of 66 months, 8 LRs were observed, with a 10-year actuarial CSS and RFS of 100% and 91%, respectively.

In a recent retrospective study of the same group, in which 586 patients treated with BCS + RT were analyzed, the risk of LR was found to be 9.6% at 10 years. The risk of LR with respect to a number of known prognostic parameters (age, tumour size, nuclear grade) was evaluated. Only age resulted to be a statistically significant prognostic factor in the univariate analysis ($P = 0.0009$). The actuarial 10-year OS and CSS were 98.5% and 99%, respectively (data submitted for publication).

2.1. Meta-Analysis of Retrospective Studies. In 1999, Boyages et al. [2] published a meta-analysis of the most important retrospective studies for DCIS, that had undergone different treatments: mastectomy (1574 cases), BCS alone (1148 cases), and BCS + RT (1452 cases). The meta-analysis revealed that the relapse incidence was of 22.5% after BCS alone (with 43% invasive LR), 8.9% after BCS + RT (with 50% invasive LR), and of 1.4% after mastectomy (with 76% invasive LR). Considering only the conservative treatment, the RT reduced the relative LR risk of at least 50%. The major advantage on local control was noted in cases of DCIS with

necrosis, comedocarcinoma, high nuclear grade, and positive or "close" margins.

3. Randomized Clinical Trials

The impact of RT after conservative surgery in women with newly diagnosed DCIS has been analyzed in four prospective randomized clinical studies. The patients had undergone conservative surgery consistent of quadrantectomy, tumorectomy, or segmental mastectomy.

In three of these studies, a comparison was made between the results of BCS alone and BCS followed by breast irradiation (two arms of randomization). A 2×2 factorial design was used in the fourth study; the aim was to see the effectiveness of either adjuvant RT or hormonal therapy with Tamoxifen (TAM); allocation of patients could have happened for both treatments (RT and TAM) or just for one of the two, reserving the second as the only other choice.

The first study, the American NSABP-B-17 trial [16], randomized 818 cases of DCIS, between October 1985 and December 1990, 80.4% of which mammographically diagnosed (Table 1).

The protocol required histological negative margins; however, inking of excision margins and specimen radiography were not routinely used in that era. Thus, in a central pathology review on histopathologic specimen, uncertain or positive margins were found in 17% of the cases [17].

The cumulative incidence of ipsilateral events, with a median followup of 12 years, was of 31.7% for the control group, compared to 15.7% for the group with RT ($P < 0.000005$); 76% were true LR within the same quadrant. Considering the invasive LR, the incidence lowered from 16.8% (control group) to 7.7% (RT group) ($P = 0.00001$); while for DCIS LR, it lowered from 14.6% to 8.0% ($P = 0.001$). Neither the cumulative incidence of contralateral tumors nor the OS ($P = 0.80$) differed significantly between the two groups.

Recently, the long-term results of the NSABP B-17 and B-24 trials have been published [18]. In the NSABP B-17 study, with a median followup of 207 months, the significant contribution of RT in reducing the ipsilateral events is confirmed (Table 2).

The regional recurrence and the distant metastasis incidence are comparable in the two groups; also the contralateral tumor incidence results are very similar as well as mortality from breast carcinoma or other causes.

The evaluation of the predictive factors was referred to in a publication from 1999 [17], in which were analyzed the results of a centralized pathological revision of 623 trial cases (77% of all study cases). With a median followup of 8.5 years, in the multivariate analysis only comedo necrosis was found to be an independent predictive variable for LR. However, it was observed that within all prognostic subgroups, an overall benefit from the use of RT was maintained.

In the second study, the European EORTC-10853 [19], 1010 patients, treated between March 1986 and July 1996, were randomized; in 71% of the cases the initial diagnosis was exclusively mammographic (Table 1).

The arm with RT received a total dose of 50 Gy in 25 fractions; only 5% of the patients received an additional boost with a median dose of 10 Gy. Negative margins represented one of the inclusion criteria; however, a centralized pathologic revision of 863 of the 1010 randomized cases (85%) revealed that the margins were positive or "close" ($\leq$1 mm) for 8.5% of the cases, and not known in 13.5% cases [20].

The LR rate, with a median followup of 10.5 years, was of 26% in the control arm, compared to 15% in the RT arm ($P < 0.0001$). In the RT group was noted a decrease in the risk of invasive LR and DCIS LR of 42% ($P = 0.0065$) and of 48% ($P = 0.0011$), respectively (Table 2). The incidence of contralateral breast tumors, of regional and distant relapse, and OS demonstrated no significant difference within the two groups.

In the multivariate analysis of the prognostic factors, young age ($\leq$40 years), symptomatically detected DCIS, high nuclear grade (G2-3), solid/comedo or cribriform growth pattern, and the absence of free margins were associated with an increased risk of LR. Similarly to the findings of the NSABP B-17 trial, RT reduced the risk of LR in all prognostic subgroups considered.

The third study, the Swedish SweDCIS [21], was conducted between September 1987 and December 1999; 1046 patients out of 1067 randomized women were eligible to the statistical evaluation, with a mean followup of 8.4 years. In 823/1046 cases (78.7%), the DCIS was discovered in a mammographic screening (Table 1).

In the RT arm, treatment could be given either continuously (total dose: 50 Gy, 25 fractions) or in a split-course schedule (54 Gy given in two series with a gap of two weeks), which was administered in less than 50 cases; no RT boost was given to the tumor bed. The protocol did not require pathologically negative margins, thus in 11% of the cases, the margins were positive and in 9% they were unknown. The difference of the LR rate was significant: 27.1% in the control group compared to 12.1% in the other one. The invasive LR were reduced from 12.3% to 7.2% and the DCIS LR from 14.8% to 4.9% with RT (Table 2). The incidence of contralateral events, metastasis, and death due to breast carcinoma did not present significant differences within the two groups.

Considering the main prognostic factors, a correlation between RT effectiveness and age was noted ($P = 0.07$), more evident for women over 60 years (risk reduction of 18%) [20].

In a previous study [22] that had investigated the histopathologic risk factors for LR by a slide revision of 2 cohort cases from the trial, high nuclear grade and necrosis were associated to a major local relapse risk. RT has conferred a reduction of relapse risk in all prognostic subgroups.

The fourth study, the English, Australian and New Zealand UK/ANZ DCIS trial [23], was conducted from May 1990 in Great Britain and September 1991 in Australia and New Zealand to August 1998 (Table 1). The protocol required the complete excision of the lesion, the radiography of the surgical specimen, and the presence of free microscopic margins. In the two arms with RT (RT, RT + TAM),

Table 1: Characteristics of the prospective randomized trials.

	NSABP-B17	EORTC 10853	SweDCIS	UK/ANZ DCIS
Entry dates	1985–1990	1986–1996	1987–1999	1990–1998
Pts. randomized	818	1010	1067	1030
CS	405	503	533	508
CS + RT	413	510	534	522
Mammographic detection	80.4%	71%	78.7%	NS
Central pathological review	76%	85%	26%	0%
Negative margins required	Yes	Yes	No	Yes
Margins free	78%	83%	80%	100%
RT dose	50 Gy/25 fr.	50 Gy/25 fr.	50–54 Gy/25–27 fr.	50 Gy/25 fr.
Boost	10 Gy/5 fr. (9% of pts.)	10 Gy/5 fr. (5% of pts.)	NR	NR

Legend: Pts: patients; NS: not specified; NR: not recommended; RT: radiotherapy; CS: conservative surgery; fr.: fractions.

Table 2: Comparison of breast cancer events in prospective randomized trials.

	NSABP-B17 (17.25 yrs. median FU)		EORTC 10853 (10.5 yrs. median FU)		SweDCIS (8.4 yrs. mean FU)		UK/ANZ DCIS (12.7 yrs. median FU)	
	CS %	CS + RT%	CS%	CS + RT%	CS%	CS + RT%	CS%	CS + RT%
Ipsilateral events								
Total	35.0	19.8	26.0	15.0	27.1	12.1	19.4	7.1
Invasive	19.6	10.7	13.0	8.0	12.3	7.2	9.1	3.3
In situ	15.4	9.0	14.0	7.0	14.8	4.9	9.7	3.8
Contralateral events	7.9	9.3	4.0	8.0	5.9	6.5	4.1	3.3
OS%	86*	87*	95	95	90**	92**	97.9#	96.2#

* At 12 yrs. followup.
** Breast cancer deaths and other deaths are reported in the study.
# All trial participants included.
Legend: yrs.: years; FU: followup; OS: overall survival; RT: radiotherapy; CS: conservative surgery.

the total dose was of 50 Gy in 25 fractions, without boost on the tumor bed; in the two hormonal-therapy arms (TAM, TAM + RT), the TAM dose was of 20 mg/die for 5 years.

The recent update of the study [24] has a median followup of 12.7 years, and it contains 1694 patients, 1030 of which were assigned to randomization for RT. In such a group, the incidence of ipsilateral events was of 19.4% in the control arm and of 7.1% in the RT arm ($P < 0.0001$), with, respectively, 9.1% and 3.3% of invasive carcinomas and 9.7% and 3.8% of noninvasive ones; the incidence of contralateral tumors was of 4.1% in the control arm and of 3.3% in the RT arm ($P = 0.6$) (Table 2). Overall, there was no significant difference in the death rate within the different subgroups.

It was noted an increase in cardiovascular deaths within the patients treated with RT, with or without TAM ($P = 0.008$), although the numbers were small. Death due to breast carcinoma proved to be higher within the patients that received hormonal treatment, but the difference was not significant [24].

3.1. The Meta-Analyses of Randomized Trials. The first meta-analysis of the four randomized trials was published by Viani et al. in 2007 [25].

The overall statistical evaluation of 3665 patients pointed out a reduction in LR risk (either invasive or DCIS) of approximately 60% with the addition of adjuvant RT, compared to excision alone. Such reduction in risk was more evident in the cases with high nuclear grade and positive margins, even though it was not possible to identify a subgroup of women with low LR risk who did not need to be treated with RT. Within the two groups, no differences appeared between the incidence of distant metastasis and the OS rate. The probability of contralateral breast carcinoma proved to be 1.53 times higher in the RT arm (3.85% versus 2.5%, $P = 0.03$). In the subsequent meta-analyses, which have examined the data of the four trials after a longer follow-up period, such difference was minimal and did not prove to be statistically significant.

In 2009, Goodwin et al. [26] published a systematic review and a meta-analysis of the four trials; a more detailed version was published in the Cochrane Library [27].

From the statistical analysis, conducted on 3925 women, a significant reduction of ipsilateral events with adjuvant RT resulted (HR = 0.49; 95% CI 0.41–0.58, $P < 0.00001$). The authors investigated the role of breast irradiation in relation to some prognostic parameters: margin status, age

(>50 versus <50 years), and presence of comedo necrosis; in all the analyzed prognostic subgroups the contribution of RT was significant.

In very few cases, severe cardiovascular toxicity or the appearance of a second primary tumor was observed, but with very similar numbers within the two groups. The median followup of the trials included in the meta-analysis varied from 4.4 to 10.5 years; the authors hypothesized that with a longer followup, an increase of RT late toxicity could appear [26].

In 2010, the meta-analysis of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) was published [28]. The statistical analysis showed that RT is able to reduce the absolute risk of ipsilateral events of 15.2% at 10 years (12.9% versus 28.1%, logrank $2P < 0.00001$) and that its effectiveness does not differ significantly in relation to age, extension of the surgical procedure, association with TAM, diagnostic method, status of the margins, focality, nuclear grade, presence of comedo necrosis, architectonic pattern, and dimension of the tumor. Regarding age, a reduction of the ipsilateral events was noted in women ≥50 years of age.

The authors examined a subgroup of 291 cases out of the meta-analysis with low risk (tumor dimension ≤20 mm, negative margins and grade 1); even in such a very favourable subgroup they confirmed a significant reduction in the 10-year risk of ipsilateral events of 18.0% with RT (logrank $2P = 0.002$).

4. Prognostic Factors

Actually, there is no evidence from observational studies and clinical trials that BCS plus RT is more or less effective than BCS without RT in the presence or absence of particular adverse prognostic factors, with RT being more effective in all subsets of patients.

BCS alone, even though not detrimental in terms of survival, is a treatment at high risk of LR.

Eastern Cooperative Oncology Group (ECOG) reported a registration study (ECOG E5194) aimed to prospectively identify favorable patients with DCIS treatable with local excision alone [29]. With a median followup of 6.2 years, the 7-year rate of LR was 10.5% for the 565 patients with low- or intermediate-grade DCIS; with a median followup of 6.7 years, the 7-year rate of LR was 18.0% for the 105 patients with high-grade DCIS. On multivariate analysis, no variable was significantly associated with LR.

Another study has demonstrated similar findings for a cohort of patients treated with BCS alone [30].

Wong et al. [36] reported on 158 patients treated with wide excision alone, with a minimum negative margin width of 1.0 cm. The 5-year rate of LR was 12%; the study, therefore, was closed early because of the negative results.

4.1. Clinical Factors. The major clinical factors associated with an increased risk of LR following breast-conserving treatment for DCIS are symptomatic presentation and young patient age at diagnosis [37].

4.2. Pathologic Factors. The most frequently reported factors associated with a higher risk of LR are high nuclear grade, comedo necrosis, and larger tumor size.

In the NSABP-B17 trial, the presence of comedo necrosis was associated with a higher risk of LR, limited, however, to the group of patients treated with excision alone [18]. In that group, LR rate at 8 years was 40% for cases with moderate or marked comedo necrosis compared to 23% for patients without it.

Data published by Silverstein et al. [10] showed that margin widths of 10 mm or more have a risk of LR unaffected by nuclear grade and addition of RT. In contrast, these factors remained significant in the group of patients with small margin widths [38].

The impact of DCIS grade on LR risk appears to be related to the length of followup, as emphasized in the study of Solin et al. [5]. In this study, comedo architecture and nuclear grade 3 had a significantly higher 5-year LR rate; the difference, however, was no longer statistically significant at 10 years.

These data suggest that risk factors for noninvasive and invasive LR may not be identical, that the analysis of the combination of these events into a single group may obscure important differences and that the biological basis for noninvasive and invasive LR may be different.

4.3. Margins. Multiple retrospective studies and some clinical prospective trials have shown that achieving pathologically confirmed negative margins is associated with a decreased rate of LR. The evaluation of the involvement of the margins of excision is one of the few clinical variables that can be controlled even though the definition of a negative margin varies from study to study (1, 2, 5, or even 10 mm).

Dunne et al. [39] reported a meta-analysis of 4660 patients treated with BCS + RT from 22 studies with data on margins of resection. The odds ratio for LR was 2.56 ($P < 0.05$), 2.89 ($P < 0.05$), and 1.51 ($P > 0.05$) for a minimum negative margin width of no tumor cells, 1 mm and 2 mm on ink, respectively.

A minimum negative margin width of 2 mm was considered appropriate in the setting of adding RT after lumpectomy. On the contrary, a minimum negative margin width of 10 mm has been recommended when using lumpectomy alone [38].

In some series, a small number of patients with close or positive margins is reported. In these cases with focally close or positive margin of resection, reexcision is the preferred next step. If a reexcision cannot be performed, definitive irradiation can be delivered with a slightly higher risk of local failure. The excess risk of LR in this setting is estimated of approximately 5%–7% [39, 40].

5. Salvage Treatment for Local Recurrence

Since DCIS is associated with a low rate of mortality, analyses of the success of treatment should focus on recurrence.

One of the arguments advanced in favor of omitting radiation after BCS at the time of initial presentation is the hypothetical ability to repeat a salvage breast conservative

treatment. However, few data have been reported on this argument. Salvage mastectomy is frequently indicated following LR, particularly when reexcision would be cosmetically unacceptable, or when an adjuvant RT was previously performed.

The rate of salvage breast conservation is only 42%–52% after primary BCS and some patients can reject secondary breast conservation in favor of mastectomy. Thus, preventing LR by adding RT at the time of initial treatment may be a more important long-term strategy.

A dedicated study [41] reported 90 patients with local or local-regional recurrence as the site of first failure. Salvage surgery was mastectomy for 76/90 (84%) patients. The median followup was 5.5 years after salvage treatment; 10-year OS and CSS were 83% and 95%, respectively; 10-year rate of freedom from distant metastases was 91%.

Local and local-regional recurrences can be salvaged with high rates of survival and freedom from distant metastases. Careful followup is warranted for the early detection of potentially salvageable recurrences.

6. Particular Aspects of DCIS Irradiation

6.1. Role of the Boost. The advantage of an additional boost to the tumor bed after BCS and whole breast irradiation (WBI) for invasive breast cancer has been confirmed by controlled clinical trials [42, 43] and is now a standard of care. Whether this is applicable to patients with pure ductal carcinoma in situ (DCIS) is unclear.

The importance of a boost in the local control of DCIS has been examined in 6 retrospective studies [31–35, 44] (Table 3), while no prospective randomized study has been published so far on this issue.

In two trials, the role of the addition of a boost is studied: the BIG 3-07/TROG 07.01 and the BONBIS multicenter study [45, 46]. In both trials the accrual of the patients is still ongoing.

Of particular interest are the results of the international multicenter retrospective study by Omlin et al. [31]: 373 patients ≤45 years old were treated with BCS only (15%), BCS followed by WBI (45%), or BCS and WBI followed by a boost on the tumor bed (40%). The authors observed a progressive increase of local relapse-free survival at 10 years, starting from BCS without WBI (46%), to WBI without boost (72%), to WBI followed by boost (86%) ($P < 0.0001$).

In the multivariate analysis, margin state and RT dose resulted as independent predictive factors of local relapse-free survival; the major advantage correlated to the delivery of the boost was noticed in young women (≤39 years).

Considering the limits of this study (retrospective design, with a very long accrual period of 26 years and lacking a centralized revision of tumor-sample histology), and while waiting for the results of the randomized clinical trials in course, it would be appropriate to consider a boost after WBI for women aged 45–50 or younger.

6.2. Hypofractionated RT. Recently, a considerable interest for hypofractionated RT schedules was noted, either in the form of whole- or partial-breast treatment.

The considerable duration of the whole treatment with conventional RT (from 5 to 6.5 weeks), associated with the distance from the patients home to the Radiotherapy Centers and the long waiting lists, represents matter-of-fact criticality factors of standard breast RT.

6.2.1. Hypofractionated WBI. The efficacy of hypofractionated WBI, in the treatment of invasive breast cancer after conservative surgery, has been confirmed by retrospective studies and by some recent randomized trials, which account excellent results both in terms of local-regional control and cosmetic outcome [47].

As long as DCIS is concerned, so far only two prospective phase I and II studies have been published [48, 49].

The study of Constantine et al. [49] is the only one that included exclusively patients with mammographically detected pure DCIS (59 cases) treated with hypofractionated WBI, for a total dose of 42 Gy in 15 fractions. With a still limited followup (36 months) no LRs or contralateral tumors were found.

The study of Freedman et al. [48] examined together women with early invasive carcinoma and with DCIS. The patients underwent a treatment of the whole breast with IMRT, at a total dose of 45 Gy in 20 fractions and a concomitant boost on the tumor bed to a total dose of 56 Gy (2.8 Gy/fr. in 20 fractions). To-date, only data relative to acute toxicity and cosmetic results have been published.

Also some retrospective studies [35, 44, 50, 51] show optimal results in terms of local control in DCIS with hypofractionated treatment.

No phase III prospective study has been published until now; in 2007, the above-mentioned international multicenter BIG 3-07/TROG 07.01 trial was initiated, and it confronted both the conventional RT schedule versus the hypofractionated one, and the boost versus no-boost delivery [45, 46]. The patients' accrual has not been closed so far: some years are needed before the results can be published.

6.2.2. Partial Breast Irradiation (PBI). PBI has been widely proposed as the treatment for early-stage invasive breast cancer; options include brachytherapy techniques (using either the interstitial catheters or the intracavitary device MammoSite), external-beam RT (3D-CRT or IMRT), and intraoperative radiotherapy.

It seems more controversial when it is used to treat DCIS, based on the knowledge of the growth pattern of this tumor within the complex ductal-lobular system of the breast [52].

According to a recent Consensus Statement of the ASTRO (American Society for Radiation Oncology) [53], which has established the criteria for the inclusion of PBI, outside the clinical trials, the partial irradiation for pure DCIS is to be evaluated with caution if the tumor diameter is ≤3 cm and is not indicated if the diameter is >3 cm. Therefore, few studies have documented the efficacy of PBI in treating DCIS so far [54].

The American Society of Breast Surgeons (ASBS) has recently published an update on the DCIS case studies included in the MammoSite Registry Trial, that represents the widest prospective database published until now [55].

Table 3: The influence of the boost on local control.

Studies	N. of pts.	Median age (y)	Positive margins %	Necrosis %	Median FU (months)	LR %
Omlin et al. [31]						
Boost	150	41*	7	32	72	14**
No boost	166		4	41		28**
Yerushalmi et al. [32]						
Boost	20	58	/	/	81	15
No boost	55	/	/	/		12.7
Julian et al. [33]						
Boost	692	53	21	52	168	13.8
No boost	877		15	45		14.3
Monteau et al. [34]						
Boost	147	53	50	60	89	9.3^
No boost	55		74	64		9.6^
Wai et al. [35]						
Boost	144	56	29	46	112	9*
No boost	338	55	12	55		6*
Wong et al. [44]						
Boost	79	58	5	56	46	0
No boost	121		0.8	49		6

* All < 45 years, ** 10-year LR, ^ 7-year LR, # Reexcision for close (<2 mm) margins.
Legend: pts.: patients; (y): years; FU: follow up; LR: local recurrence.

For 194 patients, with a median followup of 54.4 months, the 5-year actuarial LR rate is of 3.39% and the cosmetic results are favorable in 92% of the cases.

In 2005, a phase III prospective, randomized, multicenter study, NSABP B-39/RTOG 0413, was started [45, 54]. It compared WBI to PBI. Patients with DCIS or with stage I or II invasive carcinoma ($T \leq 3$ cm), N− or N+ (≤3 N+), are being treated with lumpectomy and then randomized to either WBI (±boost) or PBI with one of the 3 following techniques: interstitial multicatheter brachytherapy (34 Gy–3.4 Gy/fr, BID), brachytherapy with MammoSite (34 Gy–3.4 Gy/fr, BID), 3D-CRT (38.5 Gy–3.85 Gy/fr, BID).

The results of this trial will be very important in finding out the long-term efficacy of PBI, both for invasive carcinoma and DCIS.

It should be noted that PBI does not represent a therapeutic standard, neither for invasive carcinoma, nor for DCIS; the randomized studies in progress will have to evaluate the relapse risk, the cosmetic results, and long-term toxicity.

7. Conclusions

Randomized trials provide consistent evidence that DCIS treated with breast-conserving surgery plus radiation compared to BCS alone results in a reduction of noninvasive LR and of invasive LR by approximately 50%. As breast cancer specific survival after DCIS is uniformly excellent, the major measure of treatment effectiveness has generally been the LR rate.

Subset analyses of randomized controlled trials do not point out to differential effectiveness of surgery versus RT in the presence of some adverse prognostic factors. This suggests that treatment alone may not eliminate the adverse prognosis. However, it also suggests that for patients with adverse prognostic features, treatment may be particularly important.

Studies of new irradiation modalities (PBI, hypofractionation) in DCIS patients are currently ongoing and deserve further attention.

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Clinical Study

No Excess Mortality in Patients Aged 50 Years and Older Who Received Treatment for Ductal Carcinoma *In Situ* of the Breast

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Background. The incidence of ductal carcinoma *in situ* (DCIS) has increased at a fast rate.The aim of this study was to assess the incidence and treatment in the Netherlands and estimate the excess mortality risk of DCIS. *Methods*. From the Netherlands Cancer Registry, adult female patients (diagnosed 1997–2005) with DCIS were selected. Treatment was described according to age. Relative mortality at 10 years of follow-up was calculated by dividing observed mortality over expected mortality. Expected mortality was calculated using the matched Dutch general population. *Results*. Overall, 8421 patients were included in this study. For patients aged 50–64, and 65–74 an increase in breast-conserving surgery was observed over time ($P < 0.001$). For patients over 75 years of age, 8.0% did not undergo surgery; this percentage remained stable over time ($P = 0.07$). Overall, treated patients aged >50 years experienced no excess mortality regardless of treatment (relative mortality 1.0). *Conclusion*. The present population-based study of almost 8500 patients showed no excess mortality in surgically treated women over 50 years with DCIS.

1. Introduction

Carcinoma *in situ* of the breast is defined as abnormal proliferation of epithelial cells that do not trespass the basal membrane of the breast ductal or lobular system and consist of a heterogeneous group with different types of histology and also different prognosis [1]. The incidence of ductal carcinoma *in situ* (DCIS) has increased significantly in all parts of the world including the Netherlands, mainly due to the introduction of breast cancer screening. The biologic behavior of DCIS detected by mammography is unclear [2]. Few treated patients will ultimately die of breast cancer; however, despite the relatively benign nature of DCIS, patients commonly undergo mastectomy [2–4]. The risks of overdiagnosis and overtreatment have been discussed in several studies [2, 3, 5]. Nonetheless, some patients with DCIS have a less benign course than other patients, and it is still not possible to identify which DCIS lesions will progress to invasive carcinoma and in what time interval [6]. Besides, although DCIS is thought of as an early-stage cancer, lesions can be quite large [6].

Most clinical series have focused on the risk of breast cancer recurrence, rather than risk of death per se [3]. Population-based reports of actual deaths from breast cancer in women with DCIS are scarce, but show little excess mortality [7, 8]. The mass mammographic screening program in the Netherlands started in 1990/1991 for females aged 50–70 years; in 1997 the upper age limit of the screening program was increased to 75 years. The aim of this study was to assess the incidence and treatment of patients with DCIS in the Netherlands from 1997 to 2005 and to calculate the number of observed deaths versus the number of expected deaths based on the general population to estimate the excess mortality risk of patients diagnosed with DCIS.

Table 1: Characteristics of the population with ductal carcinoma *in situ* (DCIS) 1997–2005.

Variable		Age (years)				
		<50	50–64*	65–75*	>75	Total
		N (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)
Period	1997–1999	546 (33.2)	1196 (29.1)	529 (27.0)	232 (32.3)	2503 (29.7)
	2000–2002	511 (31.1)	1327 (32.5)	723 (36.9)	245 (34.1)	2806 (33.3)
	2003–2005	587 (35.7)	1574 (38.4)	709 (36.1)	242 (33.6)	3112 (37.0)
Grade	I	220 (13.4)	482 (11.8)	278 (14.2)	120 (16.7)	1100 (13.1)
	II	391 (23.8)	987 (24.1)	507 (25.8)	146 (20.3)	2031 (24.1)
	III	644 (39.2)	1726 (42.1)	712 (36.3)	177 (24.6)	3259 (38.7)
	Unknown	389 (23.6)	902 (22.0)	464 (23.7)	276 (38.4)	2031 (24.1)
Total		1644	4097	1961	719	8421

* Invited for mass screening program in the Netherlands.

2. Methods

2.1. Study Population. PALGA, the nationwide Dutch network and registry of histo- and cytopathology, regularly submits reports of all diagnosed malignancies to the regional cancer registries. The national hospital discharge databank, which receives discharge diagnoses of admitted patients from all Dutch hospitals, completes case ascertainment. Trained cancer registry personnel collect data on diagnosis, staging, and treatment from the medical records, including pathology and surgery reports, using the registration and coding manual of the Dutch Association of Comprehensive Cancer Centers. All data from the regional cancer registries are merged into the Netherlands Cancer Registry (NCR). From the NCR database, adult female patients with DCIS diagnosed between 1997 and 2005 were selected ($n = 8421$). Patients with a history of other malignancies were excluded. Histopathology was according to the national protocols in the Netherlands (http://www.oncoline.nl/); central review of the histopathology was not performed. DCIS was defined according to these protocols, and microinvasion (T1mi) was not included.

2.2. Statistical Analysis. Age was divided into younger than 50, 50–64, 65–75, and 75 years and older where the first and last groups were not invited for screening in the selected period. Treatment was assessed and stratified for age. Changes over time in treatment were studied using chi-square tests or linear regression analysis. Vital status was established directly from the patient's medical record or, in case of missing values through linkage of cancer registry data with the municipal population registries which record information on their inhabitant's vital status. As cause of death is not known in these cancer registry data, we used relative mortality. Relative mortality for 10 years of follow-up in the cohort was calculated by dividing observed mortality in the cohort at 10 years and expected mortality. Expected mortality was estimated based on the corresponding (age, sex, and year) general population (national life tables). National life tables were obtained from Statistics Netherlands. Mortality was stratified for age (to assess differences in young and elderly patients) and treatment. The aim of the stratification in treatments was not to compare treatments between strata as this would not be possible due to confounding by indication. Instead, we aimed to assess excess mortality over strata for each surgical treatment group.

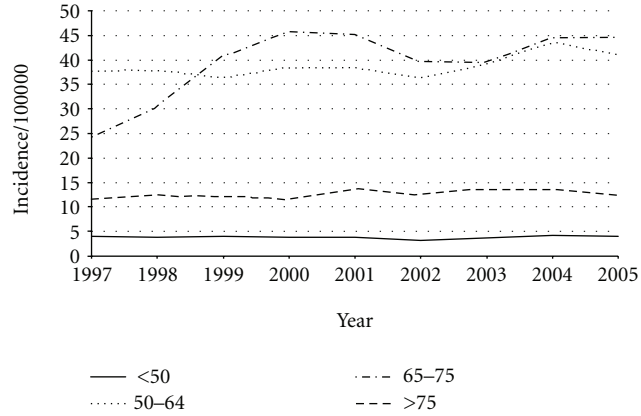

Figure 1: Incidence per 100 000 of DCIS in the Netherlands.

3. Results

Overall, 8421 patients with DCIS were included in this study. Table 1 shows the characteristics of the study population. Overall, almost half of all DCIS was diagnosed in patients aged 50–64 years. Figure 1 shows the incidence per 100 000 in the Netherlands over the period 1997–2005. The incidence for patients under 50 years remained stable (range 3.1–4.1 per 100 000). Incidence for patients aged 75 years and older remained stable around 12 per 100 000 (range 11.7–13.7 per 100 000). The incidence slightly increased for those aged 50–64 years from 37.8 to 41.0 per 100 000 and almost doubled for the age group 66–74 from 24.4 to 44.6 per 100 000.

Table 2 shows the treatment for patients with DCIS in the Netherlands according to age and period of diagnosis. Patients younger than 50 years often underwent mastectomy (range 55.7% to 60.5%) or breast-conserving surgery (range 38.9% to 46.3%). Over all the years, only 0.6% did not undergo surgery. Patients aged 50–64 and 65–74 more

Table 2

(a) Surgical treatment for DCIS over time in the Netherlands. (b) Adjuvant radiotherapy, over time, for patients with DCIS undergoing breast conserving surgery (BCS) or mastectomy

Age		1997–1999	2000–2002	2003–2005	*P* value (years)
Distribution of type of surgery over time (%)					
<50	BCS	38.9	46.3	43.6	0.4
	MAST	60.5	53.1	55.7	
	No surgery	0.6	0.6	0.7	
50–64	BCS	50.6	56.4	60.7	**<0.001**
	MAST	48.6	43.4	38.2	
	No surgery	0.8	0.2	1.1	
65–74	BCS	50.3	52.6	62.6	**<0.001**
	MAST	48.8	46.2	36.8	
	No surgery	0.9	1.2	0.6	
≥75	BCS	37.1	43.4	44.8	0.07
	MAST	55.6	50.9	45.3	
	No surgery	7.3	5.7	9.9	

(b)

Age	1997–1999	2000–2002	2003–2005	*P* value (years)
Breast-conserving surgery (radiotherapy %)				
<50	52.3	59.0	71.7	**<0.001**
50–64	46.4	69.3	81.6	**<0.001**
65–75	41.9	60.0	82.4	**<0.001**
>75	26.3	36.4	51.9	**<0.001**
Mastectomy (radiotherapy %)				
<50	2.0	2.3	5.6	**0.004**
50–64	1.8	3.0	1.9	0.8
65–75	1.4	4.1	1.2	0.6
>75	0	1.7	1.9	0.2

often underwent breast-conserving surgery, and this proportion significantly increased over time ($P < 0.001$). For the elderly patients ≥75 of age, 7.6% did not undergo surgery, half (50.4%) underwent mastectomy and 42.0% underwent breast-conserving surgery. Although there was a trend towards more breast-conserving surgery over time, this trend did not reach statistical significantly ($P = 0.07$). For all ages, adjuvant radiotherapy after breast-conserving surgery increased over the years (all P values < 0.001). In the last period (2003–2005) the highest percentage of women receiving radiotherapy was in the age 65–75 (82.4%) and the lowest in the elderly of 75 years and older (51.9%). Radiotherapy after mastectomy was performed in 3.4% for the patients younger than 50 years and increased over time from 2.0% to 5.6% ($P = 0.004$). In the other age groups, the proportion of patients undergoing radiotherapy after mastectomy was lower (2.2% for 50–64 years, 2.4% for 65–75, and 1.2% for the patients aged 75 years and older, resp.) and did not change significantly over time.

Table 3 shows the observed mortality, the expected mortality based on the general population, and the excess mortality as the ratio of the observed and expected mortality according to age and treatment (patients who received no surgery excluded). As radiotherapy after mastectomy was rarely given, mastectomy with or without radiotherapy were merged. In patients who underwent breast-conserving surgery (with or without radiotherapy) observed mortality did not significantly exceed expected mortality resulting in ratios around 1.0. For the younger patients who underwent mastectomy, a significant relative mortality was recorded (2.6; $P < 0.001$). For all strata of patients over the age of 50 years who underwent mastectomy, observed and expected mortality were close resulting in a relative mortality of around 1.0. Overall, all surgically treated patients aged 50 years and older experienced no excess mortality due to DCIS (ratio of 1.0). All ages combined, 704 deaths within 10 years were observed versus 692.1 expected based on the general population with a ratio of 1.0 expressing no excess mortality of DCIS in the Netherlands.

4. Discussion

Due to the introduction of breast cancer screening, incidence of DCIS has increased dramatically in the last years. Despite the increasing incidence not many population-based reports

Table 3: Mortality (10 years) of the surgically treated patients with DCIS as compared to the general population according to age, stratified by treatment.

Treatment	Mortality	<50 years	50–64 years	65–75 years	>75 years	Overall
BCS+RT	Observed	7	34	52	24	117
	Expected	5.2	47.5	67.4	26.9	147
	Relative mortality	1.4	0.7	0.8	0.9	**0.8***
BCS-RT	Observed	6	36	57	71	170
	Expected	3.8	29.4	49.6	74.5	157.3
	Relative mortality	1.6	1.2	1.1	1.0	1.1
MAST	Observed	29	61	100	119	309
	Expected	11.1	63.3	102.2	131.0	307.5
	Relative mortality	**2.6*****	1.0	1.0	0.9	1.0
Overall	Observed	44	156	233	271	704
	Expected	21.6	154.6	243.7	272.2	692.1
	Relative mortality	**2.0*****	1.0	1.0	1.0	1.0

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. Median follow-up: 5.9 years (range 1.2–10.9).

are available that report mortality in this group of women. The present population-based study of almost 8500 patients in the Netherlands diagnosed between 1997–2005 shows that excess mortality was observed for patients younger than 50 years. However, no excess mortality in surgically treated women over 50 years with DCIS was observed. This means that after the diagnosis and treatment of DCIS the women experienced a similar mortality as age and year matched women in the general population.

4.1. Treatment. Understanding the care received by women with DCIS is important since it is highly curable, its incidence is rising (from 4.9 (1989) to 18.6 (2008) per 100 000), and it is often detected in otherwise healthy women and there is a possibility of overtreatment [9]. Overall, 45% of the women in the Netherlands underwent mastectomy for DCIS. In many such patients, mastectomy may have been medically appropriate, based on patient preferences or the underlying practice of individual surgeons or institutions [2].

Elderly 75 years or older did not undergo surgery in 7.6%. The reasons for this are unclear, but the result is probably explained by patients who are unfit for surgery due to many comorbidities or patient preferences [10]. Although mastectomy results in a cure rate approaching 100%, this may be overtreatment for some patients, particularly those with small, mammographically detected lesions [11]. Moreover, there are no randomized studies demonstrating that mastectomy is better than conservative surgery followed by radiotherapy for patients with DCIS [1]. The role of radiotherapy after breast-conserving surgery is supported by large randomized studies for improvement of local control; however, none of these studies showed an improvement in survival or decrease in the risk of distant metastases [1, 12–14]. A recent overview of the randomized trials of radiotherapy in DCIS showed that radiotherapy reduced the absolute 10-year risk of ipsilateral recurrent DCIS by 8.4% and of ipsilateral invasive cancer by 8.5% (both $P < 0.00001$) [15]. However, after 10 years of follow-up there was no significant effect on breast cancer mortality, mortality from causes other than breast cancer, or overall mortality. In the present study administration of adjuvant radiotherapy after breast-conserving surgery increased through the years for all ages, however, remained lower for the elderly aged 75 years and older. The identification of low risk groups within the elderly patients in whom radiotherapy can be omitted as well as the development of newer radiation techniques should be a priority [1].

4.2. Mortality. In the present study, data concerning the cause of deaths was not available. However, we were able to estimate the excess mortality by comparing the mortality in the cohort to mortality in the general population (matched for sex, year, and age). The present study showed no excess mortality as compared to the general population in patients who underwent surgery. Patients who were not surgically treated were excluded from this analysis as they are probably considered to frail and by such are not comparable to the general population. As far as we know, there is only one published population-based report of the likelihood of breast cancer death among women with DCIS ($n = 7072$) [3]. Breast cancer deaths were assessed in two groups based on the introduction of screening mammography (1978–1983 and 1984–1989). Among women diagnosed in the early period, 1.5% died of breast cancer within 5 years and 3.4% in 10 years; among the women diagnosed in the latter period 0.7% died of breast cancer within 5 years and 1.9% in 10 years. The study of Ernster et al. reported a 10-year standardized mortality ratio of 1.9 (95% CI 1.2–2.3). Direct comparison of the numbers is however not possible as the study of Ernster calculated the standardized mortality ratio and the present study the estimated excess (relative) mortality. The latest numbers in the study of Ernster et al. were from 1984–1989 while the present study describes 1997–2005. Diagnostic precision (by introduction of the digital mammography) has probably improved in that period so that patients are less likely to have unrecognized microinvasive breast cancer or the proportion of detected DCIS with low malignant potential has increased [3]. This could also possibly reduce

the excess mortality due to breast cancer in our cohort as compared to Ernster et al.

As almost all women were treated surgically, it is impossible to know from these data the extent to which the low excess mortality from breast cancer among women with DCIS results from effective treatment or reflects the relative benign nature of the disease or probably both [3]. Remarkably, we did find an excess mortality in the younger patients (<50 years) treated with mastectomy. It could be that a large proportion of this group are BRCA1/2 carriers; however we have no information to verify this. Mortality was stratified for age (to assess differences in young and elderly patients) and treatment. The aim of the stratification in treatments was not to compare treatments between strata as this would not be possible due to confounding by indication. Instead, we aimed to assess excess mortality over strata for each surgical treatment group. In the present study we had no data concerning recurrences in individual patients. However, despite the fact that some of these women would have experienced a recurrence, excess mortality due to that recurrence is presumably low. Approximately half of the recurrences are not invasive and can be cured with additional surgery [1]. Furthermore, patients who present with invasive cancer have also a low risk of distant disease [1].

For some ages excess mortality was below 1.0 (observed mortality did not exceed expected mortality) indicating that women with DCIS represent a generally healthy subgroup of the population which was also confirmed in the study of Ernster et al. [3]. Women who present for mammography may have healthier lifestyles than other women; studies have shown that women who undergo regular screening are more socioeconomically advantaged and practice more preventive health behaviors than women who do not [3, 16, 17]. Moreover, breast cancer is more often diagnosed in women with a higher socioeconomic background.

In conclusion, the present population-based study of almost 8500 patients in the Netherlands shows no excess mortality in surgically treated women over 50 years with DCIS; observed and expected mortality were almost equal resulting in a relative mortality due to the DCIS of 1.0.

Conflict of Interests

No conflict of interest has been declared by any of the authors.

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Review Article

Intraductal Proliferative Lesions of the Breast—Terminology and Biology Matter: Premalignant Lesions or Preinvasive Cancer?

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Morphological criteria for the diagnosis of intraductal proliferative lesions of the breast have been an object of research and much controversy, and its terminology is rather confusing. Knowledge of the molecular aspects of this disease probably necessitates further research to clarify if these entities can be identified as breast cancer precursors or as a malignant preinvasive disease. These issues are of great interest not only for their biological implications, but also to the clinician who must understand the disease and direct therapies. Molecular studies have shown that epitheliosis (usual ductal hyperplasia) is not monoclonal, while malignant lesions (atypical ductal hyperplasia, flat epithelial atypia, low-grade and high-grade intraductal carcinoma) constantly show these characteristics. These malignant lesions, classified with a DIN grading system (ductal intraepithelial neoplasia), are not obligate precursors of invasive ductal carcinoma and do not represent different evolving grades in a linear model of cancerogenesis. Breast cancerogenesis probably has different pathways with different morphologic precursors.

1. Introduction

Intraductal proliferative lesions (IPLs) of the breast are confined to the duct-lobular system, originating from the terminal duct-lobular unit (TDLU) with different cytological and architectural patterns of proliferation. They are characterized by an increase in the number of cells perpendicular to the basement membrane resulting in total alteration and distension of the normal unit structure of the breast without increasing in number [1].

Both a lobular and a ductal type of epithelial proliferation of TDLU are recognized. While the first type is quite monomorphic, intraductal proliferations show a wide variety of heterogeneous cytological aspects and architectural patterns.

In the past several decades, there has been a wide discussion among pathologists worldwide regarding classification and grading of IPLs, with the aim to establish various risk categories. Despite these efforts, a high interobserver variability among pathologists regarding the diagnosis of IPLs as well established [2].

Criteria for diagnosis of IPLs by morphological means (Hematoxylin and Eosin and immunohistochemistry stains) are both qualitative (cytological and architectural changes), and quantitative. Diagnostic variability is not only due to interpretation of different patterns, but also to the difficulty in recognizing atypical cells isolated or in small clusters in TDLU.

In this regard, there are several open questions in the literature, including the minimum threshold for grading, the risk of progression for different type of lesions, and the relationships between normal epithelium, IPLs, and invasive ductal carcinoma (IDC). Furthermore, it is unclear whether different types of IPLs are progressive steps of the same process or represent independent lesions leading to different malignancies. In the last few years, there have been numerous studies in this field, and several answers have been suggested to these questions.

These issues are of great interest not only to those involved in basic research, but also to the clinicians, because each type of lesion has different propensity for progression to local relapse and invasive disease. Therefore, understanding the biology of these lesions is paramount, and will contribute to a better delineation of appropriate guidelines for surgical treatment, as well as adjuvant and diagnostic recommendations.

2. Terminology and Historical Aspects

The term utilized by Azzopardi [3] for benign epithelial hyperplasia was *epitheliosis*. This term found little agreement among pathologists and has gained much wider acceptance in Europe than in North America. The alternative terms in the past were *papillary proliferation* and *papillomatosis*, because it can form "tongue-like" projection into ductal lumina, but without the connective core in papillae seen in papillary lesions of other organs. To date, epitheliosis appears a correct term because it includes the various patterns of benign proliferation, as fenestrated, solid, or papillary aspects. In recent years, the term *Usual Duct Hyperplasia* (UDH) [4] has been utilized for these lesions.

Epitheliosis is a condition that has to be distinguished from in situ well-differentiated, low-grade carcinoma (LG-DCIS). The criteria for diagnosis have been well described by Azzopardi [3]. Two cell types are distinguishable in epitheliosis, epithelial, and myoepithelial, which have divergent differentiation. Immunohistochemical stains (p63, actin, calponin) are useful to detect myoepithelial cells in the lesion (Figures 1(a) and 1(b)). In epitheliosis, there is little distension of TDLU, few calcifications (not in granular form in necrotic debris), and absence of necrosis. A particularly complex pattern is the *infiltrating epitheliosis* [3, 5], previously described as *sclerosing adenosis with pseudo-infiltration* [6]. The so-called *sclerosing papillary proliferation* of Fenoglio and Lattes [7] probably represents the same entity. The hyperplastic epithelial structures are irregulars, distorted by an elastotic and sclerotic stroma.

The hallmarks of LG-DCIS are architectural and cytological aspects. Myoepithelial cells cover the neoplastic ducts but are not present in the neoplastic proliferation (Figures 3(a) and 3(b)). Intraluminal or intraepithelial calcification, as calcific bodies, are frequent. The solid form of LG-DCIS has the same cytology. Another type of LG-DCIS was referred to by Azzopardi [3] as *type 2* or *monomorphous clinging carcinoma* (Figure 2). This pattern is particularly difficult to recognize, because the change is only cytological. One or few layers of columnar, atypical cells, define the lumen of variously larger TDLU. Pathologists have been much more reluctant to accept Azzopardi's second type of clinging carcinoma as a type of DCIS, particularly in the United States. This type of LG-DCIS is referred to also as *atypical cystic lobules*, *atypical lobules type A*, *atypical columnar change,* [8] and, in recent years, *flat epithelial atypia* (FEA) [4].

A "borderline" entity, between UDH and LG-DCIS, is controversial. Historically, there are two opposing approaches. The first viewpoint entails sharp demarcation between UDH and LG-DCIS, without intermediate lesions. Azzopardi said "...names like *atypical hyperplasia* should be avoided as far as possible." The second viewpoint entails the existence of a continuum between hyperplasia and LG-DCIS, with different risk of progression for different grades of proliferation and atypia. Page et al. [9, 10] established two grades of hyperplasia, including *atypical hyperplasia*. Atypical hyperplasia is diagnosed when some features of LG-DCIS are present but other are lacking. When the duct is not completely involved, or when cytological appearance does not meet all the criteria of LG-DCIS. Other grading systems of IPLs suggested different grading of proliferation and atypia in borderline lesions [11]. The criteria proposed for the diagnosis of *atypical ductal hyperplasia* (ADH) are different: (i) lesions with cytological and architectural patterns of LG-DCIS are present, but both are not present in full flower; (ii) lesions with cytologic feature of LG-DCIS but lacking the typical growth pattern; (iii) lesions with cytological and architectural patterns of LG-DCIS but measuring in aggregate less than 2 mm [1]. Tavassoli [4] accepted the last criteria.

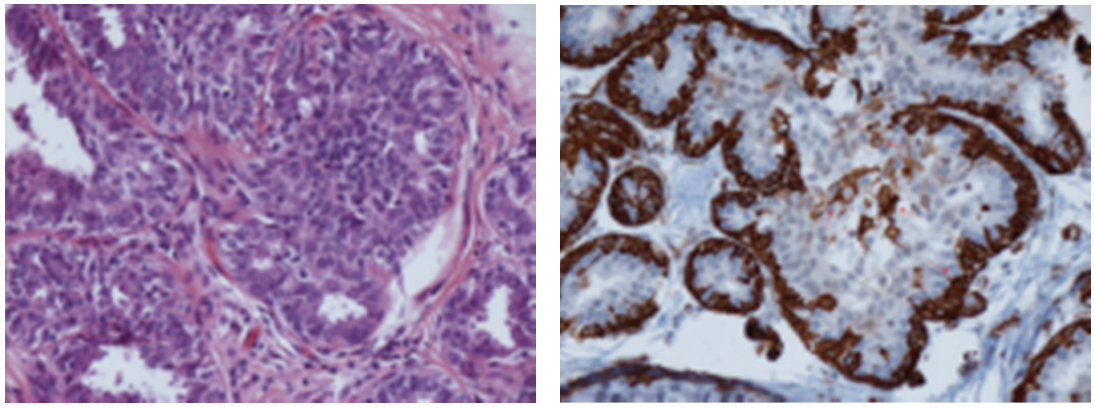
Intermediate grade DCIS (IG-DCIS) and high-grade DCIS (HG-DCIS) are obvious neoplastic lesions, graded by nuclear grade, necrosis, and architectural patterns. IG-DCIS has solid, papillary, or cribriform growth patterns, cytologically similar to those of LG-DCIS but with intraluminal necrosis (Figure 4(a)) or with intermediate cytological grade (Figure 4(b)), with or without necrosis. HG-DCIS has highly atypical cells proliferating as a single layer, or with papillary, cribriform, or solid pattern, usually with intraluminal necrosis. The HG-DCIS with solid pattern and large intraductal necrosis is referred to as *comedocarcinoma* (Figure 5). Typical granular calcifications on necrosis are present.

Rosai [2] proposed a terminology such as mammary intraepithelial neoplasia (MIN), like CIN of uterine cervix, for subjectivity and high degree of variability in interpretation of IPLs, disagreement about the criteria for definition of borderline lesions, and risk of progression of all types of IPLs. Afterwards this concept has been drawn as ductal intraepithelial neoplasia.

3. DIN System

Tavassoli [1] proposed to comprise all the IPLs in a single category, termed DIN, with various subtypes. This initial work by Tavassoli included epitheliosis or intraductal hyperplasia as DIN1a, because the risk of developing an invasive carcinoma was 1.5–2 times higher than in the general population. In the WHO book [4], UDH is separated by DIN, which includes FEA (DIN1A), ADH (DIN1B), LG-DCIS (DIN1C), IG-DCIS (DIN2), and HG-DCIS (DIN3) (Table 1).

DIN System has some advantages. It diminishes the dualism cancer/no cancer, retains separation of all different subcategories but places LG-DCIS in the same group of ADH, because it considers the differences between these lesions quantitative, not qualitative. It eliminates the term cancer, diminishing the associated anxiety and emotional



(a) (b)

Figure 1: H.E. and immunoreaction for SM-actin—epitheliosis (usual ductal hyperplasia). Intraductal proliferation with irregular, "slit-like" lumina. The immunoreaction shows myoepithelial cells (*arrows*) surrounding the duct and in the proliferation.

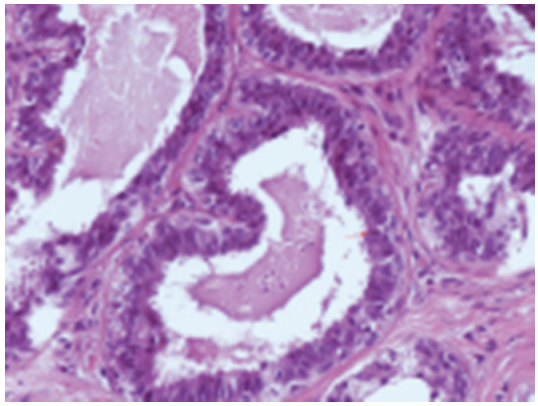


Figure 2: H.E.—flat epithelial atypia (DIN1a)—large TDLU with one to three layers of atypical ductal cells and mitosis.

stress, and it incorporates the monomorphus clinging DCIS (FEA) in the same group of ADH and LG-DCIS.

The majority of the participants in the WHO Working Group were in favour of maintaining the traditional terminology with the new DIN System [4]. This fact shows well the disagreement and scepticism of pathologists.

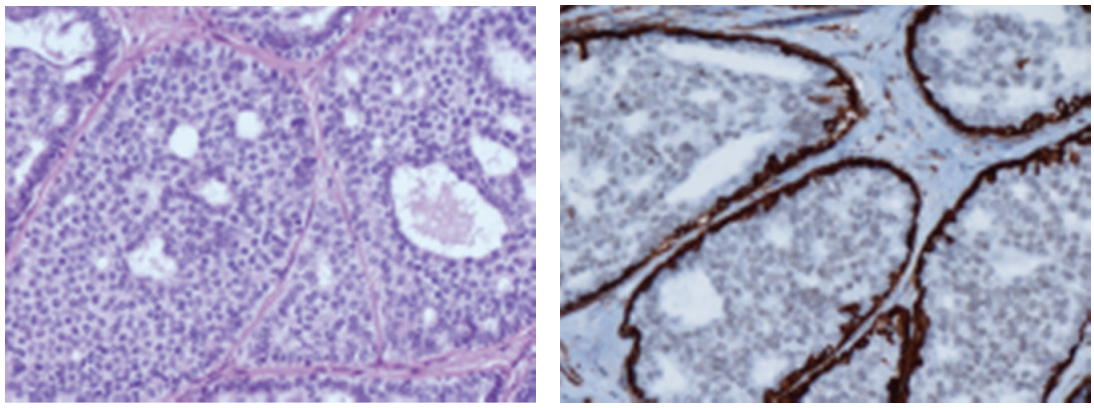
4. Genetic and Molecular Findings

In the last twenty years, there have been numerous studies to search for genetic and molecular differences or similarities between the various forms of IPLs, heterogeneous in their cytological and architectural characteristics, and between IPLs and normal TDLU and IDC. Sometimes the results seem conflicting, but a more careful analysis reveals very interesting information about histogenesis, evolution, degree of progression, and invasiveness. The apparent contradictions are related to the different methods employed, with the difficulty of performing studies on very small lesions, with the possibility of contamination by normal tissue around the lesion. Laser capture microdissection has reduced these problems, and the possibility of using very advanced methods like comparative genomic hybridization on paraffin-embedded tissues has brought to utilize archive material [12].

A multitude of methods have been utilized: immunohistochemistry (IHC), in situ hibridization (ISH), analysis of loss of heterozygosity and allelic imbalance (AI), Comparative Genomic hybridization (CGH), cDNA microarrays (MA), and Proteomics Analysis (PA). The purposes of these methods are the study of growth characteristics, the expression of oncogenes, tumor suppressor genes, and other molecules, comparison of LOH and AI between the various forms of IPLs, and IPLs versus normal TDLU, IPLs versus IDC.

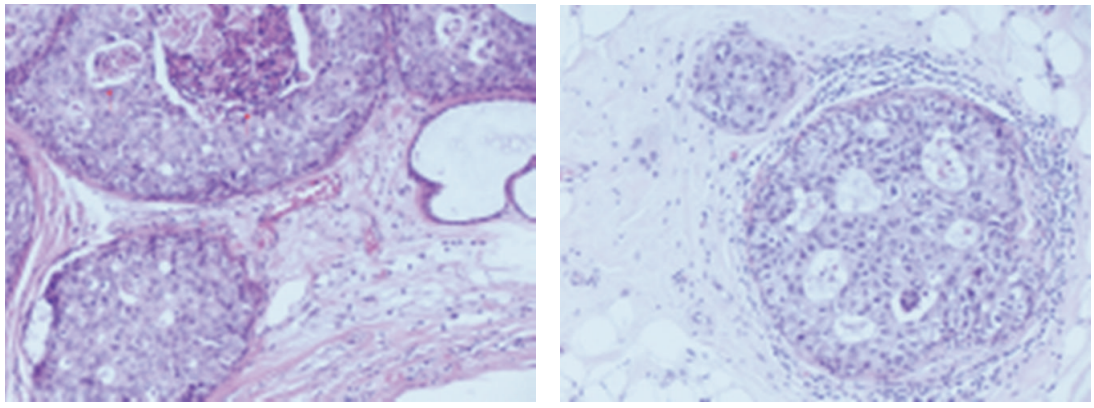
4.1. Growth Characteristics. The growth of any hyperplastic or neoplastic lesion is a balance between proliferation and cell death (apoptosis). Many researchers have studied the Proliferation Index (PI) with IHC, using antibodies marking cellular proliferative cycle like Ki67 [13]. In premenopausal women, the PI of the normal TDLU varies in different phases of the menstrual cycle. In luteal phase, it is higher than in proliferative phase. The median PI in normal TDLU is 2%, in ADH it is 5%, in DCIS it is 5%. LG-DCIS and FEA have a median PI of 5%, while in HG-DCIS it is 20%. In any case there is a continuous range from 1% and 70% from very well and poorly differentiated lesions.

ADH has a lower rate of apoptosis (0,3% versus 0,6%) and higher PI than normal TDLU; DCIS has higher apoptosis (5%) and PI than normal TDLU and ADH. Apoptosis varies from 1% to 5% among LG-DCIS and HG-DCIS, and it represents a continuous variable [14]. Higher cellular death in high-grade lesions means that the growth is a complex phenomenon. HG-DCIS has large positive growth imbalance with a high cellular death. Disturbance of the equilibrium between cell proliferation and cell death is the result of numerous alterations of growth regulating mechanisms involving sex hormones, oncogenes, and tumor suppressor genes.



(a) (b)

Figure 3: H.E and immunoreaction for SM-actin—low grade ductal in situ carcinoma (DIN1c). Cribriform type of intraductal proliferation with round, regular lumina, monomorphic round nuclei. Myoepithelial cells surround the duct but are not in the proliferation.



(a) (b)

Figure 4: H.E.—intermediate grade ductal in situ carcinoma (DIN2). Obvious cribriform ductal in situ carcinoma with necrosis (Figure 4(a)—*arrow*) and intermediate cytological grade.

4.2. Sex Hormones, Oncogenes, and Tumor Suppressor Genes. Estrogens, through Estrogen Receptor (ER), play a central role in growth and differentiation of normal TDLU epithelium, stimulating cell proliferation and regulating expression of other genes, like Progesteron Receptor (PgR) [15]. Two types of ER are described: ERα and ERβ. ERα is the more studied molecule. 90% of normal TDLU express ER in an average 30% of cells [14]. There is a change of expression during the menstrual cycle: in the luteal phase, the rate of positive cells is higher (40% versus 20%). In postmenopausal women, the rate is higher (50%). Nearly all cells of ADH express ER. ER is expressed in 75% of DCIS; 100% in LG-DCIS, nearly all cells, and 30% in HG-DCIS, usually in a rate of cells [14, 16].

Many molecules are studied in IPLs, but the majority of studies have not been validated [17]. Exceptions are c-erbB2 (*neu*) and p53.

In IDC, c-erbB2 (*neu*) is overexpressed or amplified in 10–20% of cases, generally HG-IDC. It plays a role in cell proliferation, is related to poor clinical outcome, is a predictive marker for responsiveness to various therapies, and promotes cell mobility [18]. In recent years, it has been one of the more studied markers in breast cancer, because it is a target for trastuzumab therapy. Normal TDLU, UDH, ADH, and FEA do not express c-erbB2 (*neu*). LG-DCIS and intermediate grade express neu in less than 10% of cases, whereas in HG-DCIS it is overexpressed in 60% of cases [19].

The more utilized method to detect expression of p53 is IHC, which is a surrogate assay for detecting mutations, because a gene with missense mutations codifies for inactivate protein. This abnormal inactive protein is accumulated in very high levels in the nucleus of neoplastic cells, and it is detectable by IHC [20]. 30% of IDC overexpress p53, and it is related to aggressive biological features and poor clinical outcome. Normal TDLU, UDH, and ADH do not overexpress p53, apart from in the Li-Fraumeni syndrome, characterized by inherited mutations. In DCIS p53 correlates

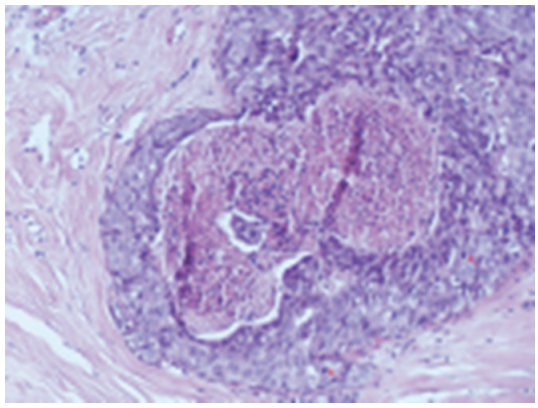


Figure 5: H.E.—high-grade ductal in situ carcinoma (DIN3). Solid intraductal carcinoma with high cytological grade and necrosis (*comedocarcinoma*) and numerous mitosis.

Table 1: Terminology of IPLs.

DIN system	Traditional terminology
Usual ductal hyperplasia (UDH)	Epitheliosis Infiltrating epitheliosis Papillomatosis Sclerosing adenosis with pseudoinfiltration Sclerosing papillary proliferation
DIN1a	Clinging carcinoma monomorphus or type 2 Flat epithelial atypia Atypical cystic lobules Atypical lobules type A Atypical columnar change
DIN1b	Atypical ductal hyperplasia (ADH)
DIN1c	Low-grade ductal carcinoma in situ (LG-DCIS) DCIS grade 1
DIN2	Intermediate-grade ductal carcinoma in situ (IG-DCIS) DCIS grade 2
DIN3	High-grade ductal carcinoma in situ (HG-DCIS) DCIS grade 3

with differentiation. It is rare in LG-DCIS and common (40%) in HG-DCIS [21].

Clark et al. [22] found by IHC analysis on tissue microarray (TMA) the same molecular classes in DCIS as in IDC [23, 24], but with different frequency. Basal-like phenotype is rare in DCIS; c-erbB2 is more frequently expressed in Luminal-like DCIS than in IDC (13,2% versus 5,2%). The mitochondrial antiapoptotic protein *bcl2* is up-regulated in LG (G1-G2) Luminal-type DCIS. The same results are in the study of Tamimi et al. [25]. Livasy et al. [26] found a higher frequency of Basal phenotype in DCIS.

Other genes and proteins are studied in IPLs and compared with IDC.

Ma et al. [27] studied five genes with quantitative RT-PCR in ADH and DCIS, upregulated or downregulated in IDC. These genes were altered in the same rate in ADH, DCIS, and IDC: for example, CRIP1 was upregulated in 7/8 ADH, in 27/30 DCIS and in 23/25 IDC, and ELF5 was downregulated in 7/8 ADH, in 28/30 DCIS and 25/25 IDC. Significant alterations in gene expression of ADH are maintained in the later stages of DCIS and IDC. Furthermore, to characterize the molecular link between DCIS and IDC, the study recognizes other clusters of genes related to infiltrative potential. These genes establish different patterns of gene expression among DCIS, which reflect different invasive potential, and there is a gene signature of DCIS, like for IDC [28].

Gillett et al. [29] studied expression of Cyclin D1 in ADH and DCIS. In IDC, expression of Cyclin D1 is more frequent in well differentiated and ER+ cases. ADH does not express Cyclin D1, but it is ER+ like LG-DCIS: in DCIS Cyclin D1 is over-expressed in 64% of cases, and it is not related to grade or to ER expression.

Schuetz et al. [30] studied genes of epithelial mesenchymal Transition (EMT) and other genes candidates to cause invasion and metastases [31]. These genes (Twist1, SPARC, MMP13, MMP11, BPAG1) are markers of transition from DCIS to IDC. Some of the proteins codified by these genes are very interesting: for example, BPAG1 is expressed in hemidesmosomes connecting epithelial cells to basement membrane. IDC cells do not contain hemidesmosomes and BPAG1 is downregulated. Matrix metalloproteinases (MMPs) can degrade different components of extracellular matrix, including laminin, fibronectin, collagen, and elastin, and are upregulated in HG-DCIS.

Porter et al. [32] and Kretschmer et al. [33] found several genes of IDC up-regulated in DCIS using SAGE (Serial Analysis of Gene Expression), TMA, quantitative RT-PCR, and IHC. Some of these genes are not related to differentiation grade (MUC1, SBP1) and probably play a role in early cancerogenesis. Other proteins, like the psoriasin (S-100A7), a calcium-binding protein that regulates cell cytoskeleton and motility, are present in comedo-type HG-DCIS.

4.3. LOH and Allelic Imbalance (AI). Two types of studies are performed: the first on IPLs in their pure form and the second on IPLs with synchronous IDC in the same breast. The strategy of the last type is to identify alterations, which may be important in the invasiveness [17]. Generally, IPLs with synchronous invasive cancer share more frequent genetic alterations with IDC than pure forms. For example, a marker on chromosome 11p (D11S988) is more frequent in all IPLs close to IDC than in IPLs without cancer [34]: morphologically normal TDLU close to IDC also shared rarely some LOH with cancer [35]. O'Connell et al. [34], assessing LOH to 15 loci on 12 chromosomes, found that 50% of ADH shared their LOH phenotypes with synchronous IDC, providing novel and compelling genetic evidence that ADH is a direct precursor of IDC. Many studies of DCIS have shown that nearly all lesions share several identical AI with synchronous IDC, providing convincing if not surprising evidence that they are evolutionarily related too [34–38]. Synchronous DCIS and IDC may occasionally

show distinct AIs, suggesting that there may also be divergent aspects to their evolution [25].

There are numerous studies on LOH in IPLs without invasive cancer.

Allelic Imbalance in UDH is rare: Lakhani et al. [39] found alterations in 0–13% of studied loci, frequently in 17q; Deng et al. [35] found alterations in different loci in 0–15%.

Moinfar et al. [40] found AI on 77% of FEA, at least in one locus 11q, 16q, and 3p. 11q and 16q are frequently involved in tubular carcinoma.

Morphological overlap between ADH and LG-DCIS is reflected at molecular level. Up to 50% of ADH contains one or more AIs among 30 genetic loci [35, 39], and they are the same of DCIS.

CGH analysis of DCIS has demonstrated a large number of alterations, including gains of 1q, 5p, 6q, 8q, 17q, 19q, 20p, 20q, and Xq, and losses of 2q, 5q, 6q, 8p, 9p, 11q, 13q, 14q, 16q, 17p, 17q, and 22q [35, 41, 42]. Some AI are more frequent and constitute hot spots: loss in 11q, 16q, 17p and 17q.

Rosenberg et al. [43] studied a series of 15 microsatellite loci in ADH and found monoclonal microsatellite alterations in 40% of cases in more than one locus, suggesting that a genetic instability plays an early role in cancer progression.

Wiechmann and Kuerer [44] characterize the differences between LG-DCIS and HG-DCIS and their risk of progression in IDC by means of the expression of steroid receptor (LG-DCIS is frequently ER/PgR positive), growth characteristics (Ki67 is lower in LG-DCIS than in HG-DCIS), expression of c-erbB2 (frequent in HG-DCIS, rare in LG-DCIS), bcl2 and p53 (the first over-expressed in LG-DCIS, the second frequently mutated in HG-DCIS), expression of psoriasin (S-100A7) and metalloproteinases (MMPs) (upregulated in HG-DCIS), and allelic imbalance (LG-DCIS has frequently gain of 1q and loss of 16q, whereas HG-DCIS shows frequently 17q12 and 11q13 amplification).

In Table 2 are reported the more frequent alterations in IPLs and IDC.

Table 2: "hot spots" in IPLs—more frequent allelic imbalances reported.

	Gains	Losses
UDH	rare	rare
ADH	1q, 16p	11p, 11q, 16q, 17p
FEA	—	3p, 11q, 16q
DCIS	1q (*LG-DCIS*), 5p, 6q, 8q, 17q, 19q, 20p, 20q *(HG-DCIS)*, Xq	2q, 5q, 6q, 8p, 9q, 11q (*HG-DCIS*),13q *(HG-DCIS)*, 14q, 16q *(LG-DCIS)*, 17p, 17q *(HG-DCIS)*, 22q

5. Discussion

One of the most controversial topics about breast pathology concerns IPL, with a wide range of phenotypic manifestations from epitheliosis to DCIS. Page et al. [9, 10] have suggested that there is a continuum between these two extremes, with an intermediate condition called ADH. Azzopardi [3], on the other hand, draws a sharp line of demarcation between hyperplastic and neoplastic lesions, and he stigmatizes: "…names like "atypical hyperplasia" should be avoided as far as possible". He himself describes a particular type of DCIS called clinging carcinoma. The low-grade clinging carcinoma (type 2 according to Azzopardi) and columnar change is named also flat epithelial atypia (FEA).

High interobserver variability among experienced pathologists in ADH interpretation is reported [2], mainly related to different proposed criteria. WHO book [4] suggests the use of dimensional criteria of Tavassoli [1]: ADH is a lesion with cytological and architectural pattern of LG-DCIS measuring in aggregate less than 2 mm.

The various IPLs have different risk of progression: UDC has two folds, ADH four folds, and LG-DCIS ten folds compared to normal breast [9, 10]. At the molecular level, rarely UDH shows allelic imbalance (AI) for one gene, whereas ADH, FEA, and LG-DCIS show frequent AIs for many genes [34–39]. Expression of high-molecular-weight cytokeratin is different between UDH and other IPLs: UDH consistently displayed the presence of a population of cytokeratin 5/6-expressing basal-type cells within the proliferative lesion, whereas ADH and LG-DCIS lacked cytokeratin 5/6-positive cells. A subset of HG-DCIS express cytokeratin 5/6: it is probably the precursor of Basal-like IDC [42]. The studies about growth characteristics (proliferative index and apoptosis) and about expression of different molecules like ER, oncogenes, and tumor suppressor genes display a substantial difference between UDH and other IPLs. ADH, FEA, and LG-DCIS, on the other hand, shares many biological characteristics with IDC [13, 14, 16, 17, 45], and microsatellite analysis shows monoclonality and genetic instability in ADH [43]. This supports the concept that UDH is a not malignant lesion, the opposite to other IPLs. ADH, FEA and LG-DCIS can be set in the same group of pre-invasive breast neoplastic lesions. DIN system, as well as proposed by Tavassoli [4], includes ADH, FEA and DCIS, not UDH.

Several data support the concept that different types of DCIS show different genetic alterations [41, 42]. Alterations at 16q are much more frequent in LG-DCIS than in HG-DCIS, in which alterations at 13q, 17q, and 20q are more frequent [4, 6, 7, 10]. Similar findings are in invasive carcinomas of low and high grade [41, 42, 46–48]. On the other hand, LG-DCIS share many molecular alterations with ADH [35, 39] and LG-IDC, and also the few studies on FEA [40] show alterations similar to LG-IDC, in particular with a very well-differentiated IDC (tubular carcinoma). These molecular studies reflect the same morphological findings: (i) it is extremely rare to find an HG-DCIS in a LG-IDC, as well as a LG-DCIS in an HG-IDC; (ii) in tubular carcinoma we see frequently an in situ component like FEA or LG-DCIS cribriform type. Also, growth characteristics and rates of expression of sex hormones, oncogenes, and tumor suppressor genes suggest that LG-DCIS is a precursor of LG-IDC and HG-DCIS is a precursor of HG-IDC [41, 42].

Table 3: Cancerogenesis models.

Linear model of progression

TDLU ⇨ UDH ⇨ ADH or FEA ⇨ LG-DCIS ⇨ HG-DCIS ⇨ IDC ⇨ Metastases

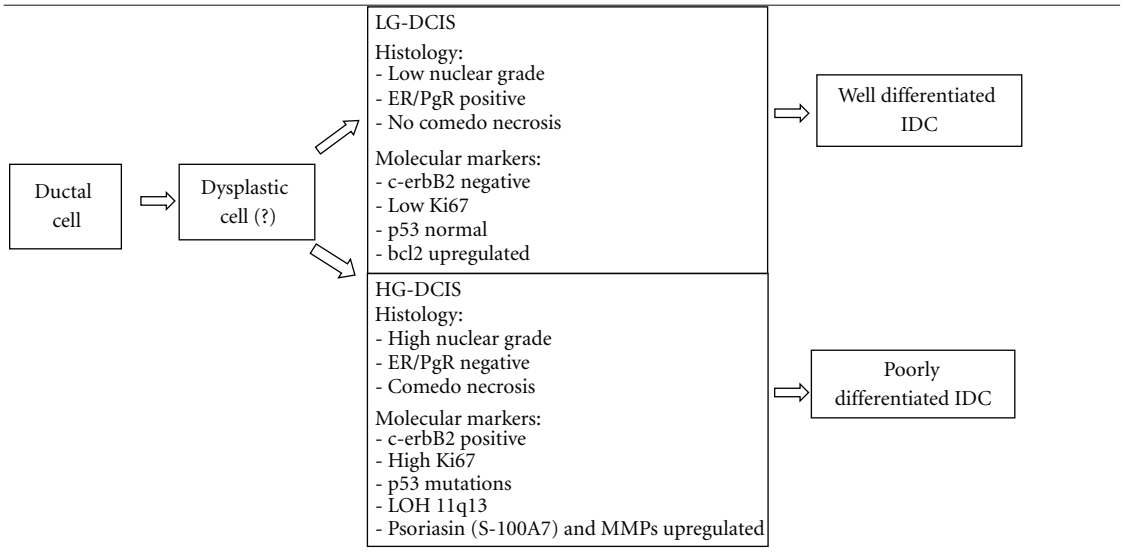
Parallel model of progression

(1) TDLU ⇨ ADH ⇨ LG-DCIS ⇨ LG-IDC ⇨ Metastases

FEA

(2) TDLU ⇨ HG-DCIS ⇨ HG-IDC ⇨ Metastases

Table 4: Classification of DCIS based on biologic potential [44].



These data suggest that there may be multiple pathways for the evolution of IPLs and IDC. In various tissues, a linear multistep progression between various preinvasive stages, which end in invasive cancer, is recognizable: in colonic mucosa, for example, there is a linear multistep model from normal epithelium to invasive carcinoma through the sequence hyperproliferative epithelium, adenoma, carcinoma, and any morphological step is related to a specific genetic alteration [49]. In breast cancer, the linear model undoubtedly oversimplifies a complex process. There is no morphological or molecular evidence that LG-DCIS progress into an HG-DCIS, or into HG-IDC. The model that results from morphological and molecular data is horizontal (or parallel), and it is done by two or several pathways (Table 3).

For this reason, the DIN system is not a progression through different grades, like the intraepithelial neoplasia in other tissue (for example, the CIN system of cervical cancer), but a classification of different intraductal neoplastic conditions, each of these are not an obligate precursor of IDC.

The DCIS classification of Wiechmann and Kuerer [44], based on biological potential to progress into IDC, shows two parallel pathways of progression with different histologic characteristics and molecular markers. Between these two pathways, there is a presumptive common progenitor, a *dysplastic cell*, not better characterized (Table 4).

In IDC, recent studies have led to a molecular classification based on the biological characteristics of the tumor rather than limited to morphological analysis. Perou [23] and Sotiriou et al. [24] identified molecular subtypes of invasive breast cancer based on an intrinsic gene signature. Many studies have aimed to identify an IHC profile that can act as a surrogate for gene array analysis, and it appears that a five-marker panel of estrogen receptor (ER), progesterone receptor (PR), c-erbB2, cytokeratin 5/6, and EGFR shows ability to categorise invasive cancers to their molecular subtype [50]. Much less attention has been focused on dissecting the biological subtypes of DCIS, and there are discrepancies in the results. Thus, whereas several studies report the existence of a basal subtype of DCIS [25, 51], one gene array study found no firm evidence of this category of DCIS or it is much less frequent [51]. There are also other discrepancies in the relative frequency of subtypes between the in situ and invasive disease. It has been recognized, for example, that there is a higher frequency of c-erbB2-positive DCIS compared with c-erbB2-positive IDC [52]. The difference in expression of c-erbB2 is actually inexplicable: the hypotheses advanced are that the expression

is switched off during invasion or that many c-erbB2-positive DCIS do not transform to IDC.

6. Conclusions

Diagnosis and reproducibility of proposed criteria of IPLs are complex. This is testified by terminological confusion, with a large number of designations for the same entity. To render the issue even more controversial, it is not clear whether some of these entities really occur in practice. Interobserver agreement in diagnosis of intermediate lesions is low. The DIN system unifies the terminology, while it may have the additional advantage to decrease the anxiety and emotional stress of patients.

Morphological complexity is reflected by the large variety of molecular findings described by a number of studies in the last twenty years. Some of these alterations are confirmed by different studies, and their comparison with different clinical entities provides much information about their nature and propensity for progression. UDH or epitheliosis is probably a benign process, while other IPLs (ADH, LG-DCIS, HG-DCIS, FEA) are neoplastic processes. ADH and FEA shares many alterations with LG-DCIS and LG-IDC, while HG-DCIS share many alterations with HG-IDC. Probably, the model of breast carcinogenesis is more complex than in other tissues, because the results of the molecular studies suggest parallel different pathways of carcinogenesis. By this point of view, the DIN system is not a progression through different additional steps, like the intraepithelial neoplasia in other tissues (e.g., the CIN system for uterine cervix cancer), but a classification of different conditions, which are not obligate precursors of IDC.

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Review Article

Ductal Carcinoma In Situ: What Can We Learn from Clinical Trials?

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Ductal Carcinoma in situ has been diagnosed more frequently in the last few years and now accounts for approximately one-fourth of all treated breast cancers. Traditionally, this disease has been treated with total mastectomy, but conservative surgery has become increasingly used in the absence of unfavourable clinical conditions, if a negative excision margin can be achieved. It is controversial whether subgroups of patients with favourable in situ tumors could be managed by conservative surgery alone, without radiation. As the disease is diagnosed more frequently in younger patients, these issues are very relevant, and much research has focused on this topic in the last two decades. We reviewed randomized trials regarding adjuvant radiation after breast-conservative surgery and compared data with available retrospective studies.

1. Introduction

Ductal carcinoma in situ (DCIS) is the fourth leading cancer among women in the United States, and its incidence has dramatically increased since the introduction of screening mammography. In the last 30 years we have witnessed a fourfold increase in its incidence [1], so that approximately one-fifth of all screen detected breast cancers are diagnosed as DCIS [2]. The relevance of this problem is evidenced by the large amount of data available in the literature, with more than 10,000 articles published on the issue, so far [3].

Interestingly, while the incidence of DCIS is increasing at a 15% annual rate in all age groups, the incidence of invasive breast cancer has been decreasing along with overall mortality for breast cancer [4].

Standard of care for surgical treatment of DCIS has long been represented by total mastectomy, with cure rates approaching 100%. Mastectomy remains indicated if the disease is too extensive to be resected with a good cosmetic outcome, in the case of inability to achieve negative margins, in the case of micropapillary DCIS or DCIS with nipple discharge, or if there are contraindications to radiotherapy (RT) in high-risk patients.

However, as breast conservation has been demonstrated equivalent to mastectomy for breast cancer patients in terms of overall survival in 6 prospective-randomized trials [5], conservative approaches have become appealing for this preinvasive disease.

It is evident that the search for the appropriate surgical treatment of DCIS is strategic, because while the disease is often multifocal, approximately 40% of recurrences are invasive [6]. Additionally, DCIS is often diagnosed in women during the "active" years of their lives, as approximately half of them become aware of this disease before the age of 60 [7], and roughly one-third before the age of 50 [3]. Therefore, while prevention of LR is a major goal of the treatment of DCIS if one wishes to maintain this disease always curative, the need to maintain a good body image for these patients cannot be understressed.

As our knowledge and understanding of DCIS has evolved in the last decades, the treatment decision-making process has become increasingly complex, and it remains one

Table 1: Randomized trials results of excision with or without RT.

Trials	NSABP B-17	EORTC 10853	UKCCR	SWE-DCIS
Patients	818	1010	1030	1046
Date	1985–1990	1986–1996	1990–1998	1987–1999
Median F/U (years)	12	10.2	4.3	5.2
Central path review (%)	76	85	79	20
LR with RT (%)	15.7	15	5.6	7
LR w/o RT (%)	31.7	26	13.6	22

Legend: F/U: followup; LR: local recurrence; w/o: without.

of the most controversial aspects in breast cancer treatment. This is well evidenced by a recent report on treatment of DCIS in the United States, describing that at the present time 30% of women with DCIS are treated with mastectomy, 40% with conservative surgery plus RT, and 30% with excision alone [8]. Additionally, data on treatment trends for DCIS in the USA have documented a shift in the last 15 years with a decrease of mastectomy in favour of breast conservation plus RT [3].

Breast conservation for DCIS is an issue of particular relevance and interest, because it is well documented that, on the other hand, mastectomy rates are on the rise in the USA as in other parts of the world [9]. Furthermore, a threefold increase of contralateral "prophylactic" mastectomy has been reported in the last decade [10], and it is recognized that DCIS is a marker for increased risk of invasive carcinoma in both breasts [11].

Several clinical factors may help to explain the tendency to implement this approach, including a more liberal use of MRI in the last few years with appreciation that the disease may be more extensive than previously recognized [12], and adoption of "conservative" mastectomies with immediate reconstruction, including nipple-sparing approaches.

The aim of the present report is to critically analyze data from randomized trials for DCIS and to compare their conclusions with data from retrospective series.

2. Randomized Trials

Five prospective randomized trials were reported in the last two decades regarding adjuvant treatment after surgery for DCIS. Four of them focused on the need of adjuvant RT after conservative surgery (Table 1), while two also investigated the addition of tamoxifen to lumpectomy plus RT.

2.1. NSABP B-17. In NSABP B-17 [13] 818 women with DCIS were randomized to undergo either lumpectomy only ($n = 403$) or lumpectomy followed by breast irradiation ($n = 410$) to a total dose of 50 Gy (9% of patients received 10 Gy boost to the tumor bed). Histologically negative surgical margins were required in both groups, however inking of margins was not routinely used. The five-year outcomes were first reported in 1993 [14] showing a 60% lower risk of ipsilateral breast tumor recurrence for patients who received RT. Subsequent updates continued to demonstrate a large benefit for lumpectomy plus radiotherapy compared with lumpectomy [15]. The 12-year local recurrence rate was 15.7% among women who underwent breast irradiation and 31.7% among women treated by lumpectomy alone ($P = 0.000005$).

2.2. EORTC 10853. In a similar trial from EORTC [16] 1010 women with DCIS were randomized to undergo either lumpectomy only ($n = 503$) or lumpectomy followed by breast irradiation ($n = 507$) to a total dose of 50 Gy. Histological negative surgical margins were required in both groups. However, at central pathology review margins were close (<1 mm) or involved in 8.5% of patients. At 10 years, patients treated with local excision alone had a LR rate of 26%, compared with 15% of LR rate in the group of excision plus RT ($P < 0.0001$).

2.3. SWE-DCIS. In the SweDCIS trial [17] 1067 women were randomly assigned to excision plus RT ($n = 526$) or excision only ($n = 520$). RT was administered continuously with 50 Gy in 25 fractions, or as a split course treatment with 54 Gy in two series with a gap of two weeks. No boost to the tumor bed was ever used. Microscopically clear margins were not mandatory. After a median followup of 5.2 years the cumulative incidence of LR was 22% in the control group and 7% in the RT group. No differences were observed in the two groups for metastases or breast cancer deaths.

2.4. UK/ANZ. In the UK/ANZ trial 1701 patients were randomly assigned to RT, and/or tamoxifen (TAM), using a two by two factorial design between 1990 and 1998 [18]. This created four subgroups: excision alone, excision plus RT, excision plus TAM, and excision plus RT plus TAM. At a median followup of 4.4 years the rate of local recurrence was 5.6% in the group with RT and 13.6% in the group without RT ($P < 0.0001$). Rate of LR was not found to be significant if tamoxifen was added to RT.

2.5. NSABP B-24. Another large randomized study (NSABP B-24) [13] investigated the addition of tamoxifen to lumpectomy plus radiotherapy in a cohort of 1804 patients treated between 1991 and 1994. The 7-year LR rate was 11.1% in the group treated with placebo and 7.7% in the group with tamoxifen ($P = 0.02$). This represented a 31% reduction in the risk of ipsilateral breast recurrences. Tamoxifen also accounted for a 53% risk reduction of contralateral breast tumors. The 7-year OS was 95% in both groups, with a no

significant increase in the incidence of endometrial cancer in the tamoxifen group (0.78% to 0.33%; $P = 0.38$).

3. Meta-Analysis

A recent meta-analysis of the four randomized trials on radiation therapy for DCIS [19] showed that the LR rates were 4.79% (82/1711) and 11.3% (221/1954) for the RT and the observation arm, respectively.

The analysis showed a 60% reduction of risk of invasive and DCIS ipsilateral breast cancer with adjuvant RT.

While the incidence of ipsilateral breast cancer recurrence did not differ in the two groups, there were more invasive ipsilateral breast cancers in the observation group (8.1%) compared to the RT arm (3.8%).

The likelihood of contralateral breast cancer was 1.53-fold higher (3.85% versus 2.5%, $P = 0.03$) in RT arm.

The meta-analysis was not able to identify a subgroup of women who would not need RT, although the absolute magnitude of benefit was greater in the groups at higher risk for local failure, such as young patients and those with clinically evident lesions.

Another recent meta-analysis by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) analyzed individual patient data for all four randomized trials [20]. A total of 3729 remained eligible for the analysis after the exclusion of patients with microinvasion, invasion, Paget's disease, or another cancer present at the time of initial diagnosis. Radiotherapy reduced the absolute 10-year risk of any ipsilateral breast event by 15.2% ($P < 0.00001$), and it was effective regardless of the age at diagnosis, use of tamoxifen, margin status, focality, grade, comedonecrosis, architecture, or tumor size.

Furthermore, the proportional reduction in ipsilateral breast events was greater in older than in younger women but did not differ significantly according to any other available factor.

Even for women with negative margins and small low-grade tumors, the absolute reduction in the 10-year risk of ipsilateral breast events was 18.0% ($2P = 0.002$). After 10 years of followup, there was, however, no significant effect on breast cancer mortality, mortality from causes other than breast cancer, or all-cause mortality.

4. Discussion

Results of these important randomized trials have been used to justify RT for all women with this disease.

Of course, RT is time consuming for the patients, may be responsible for several local side effects, and its avoidance would be desirable in patients with a low risk of recurrence. Additionally, it is well recognized that RT is associated with higher rates of complications if a mastectomy and breast reconstruction are needed in case of relapse [21, 22].

Relapse after treatment of DCIS is not rare, and a 9.8% incidence of invasive ipsilateral second events was reported in a recent analysis of 3046 patients from the Cancer Registry of Norway, with a median followup of 5 years [23]. An analysis of the outcome of 150 patients with LR after treatment for DCIS showed that 63 of them were invasive, and that the risk of death from breast cancer was 12% in that group [24].

There are several problems regarding the design of these four randomized trials. Pathologic factors affecting local control were largely unrecognized when these studies were designed and initiated.

Roughly 70% of women were randomized and treated before 1995, an era when both diagnosis and treatment was very different from current standards. Wide free margins and mammography of the excised breast tissue are now standard practice among dedicated surgeons, and whenever a positive surgical margin is found at final pathology, a reexcision is usually recommended. Neither mammography of the surgical specimen to confirm excision of all microcalcification, nor negative margins of excision were a mandatory achievement in three of the four trials. Furthermore, MRI was not an option for these women, and therefore patients were included in the study even if radiologic evidence of multifocality by current standards could not be excluded. Finally, we have entered an era of increasing awareness among women and diagnosis of smaller tumors is more often reported. Outcome of screening-detected DCIS treated with excision alone may be more favourable, and although recurrence rates of 15% at 5 years are reported, these are often successfully salvaged with breast conservation, with overall breast-specific survival of 99% [25].

In NSABP B-17 histologically negative surgical margins were required. However inking of margins was not routinely used and in 13% of cases margins were either involved or unknown. NSABP B-24 allowed entry of women with involved tumor margins and women whose mammograms showed residual calcifications as long as they were considered not suggestive of invasive cancer. In fact, in this trial approximately one quarter of patients had either involved or uncertain tumor margin status. In the EORTC trial, central pathology review of margins showed that they were close (<1 mm) or involved in 16% of patients. In the Swe-DCIS trial microscopically clear margins were not mandatory, and approximately 10% of patients had pathologically involved margins.

Furthermore, in NSABP B17 both DCIS and lobular carcinoma in situ were considered eligible. Treatment of lobular carcinoma in situ is very different today, as we recognize it as a different pathological entity from DCIS, with different risks of relapse and issues for local control, at least for the low- and intermediate-grade varieties.

These problems limit the ability to apply the results of these trials to patients who undergo what is now considered optimal surgery with total pathologic evaluation. In fact patients with positive margins appeared to benefit the most from adjuvant radiation therapy, and this has been proposed as a possible explanation for the differences between these trials and other retrospective experience [26].

Furthermore, preoperative evaluation of the extent of disease is changing, an important issue given the finding of the UK Sloan Project that in 30% of patients undergoing BCS for DCIS preoperative imaging underestimates the extent of disease, resulting in a requirement for further treatment [27].

Silverstein reported his experience and found that in patients without RT, and with a careful pathological evaluation and achievement of negative margins of almost 1 cm in all direction, LR rates were comparable to those of patients treated with RT in those randomized trials [28].

In a classic work from Silverstein [28] the 10-year actuarial LR rates after BCS with or without RT were 20% and 28%, respectively ($P = 0.06$). It is noteworthy that more patients had close (<1 mm) margins in the RT group compared to the group treated with excision alone (35% versus 19%).

In this study tumor size, nuclear grade, margin width, comedonecrosis and patient age were predictors of local recurrence. This finding is very similar to a recent meta-analysis involving 44 studies on the tumor characteristics as predictors of local recurrence after treatment of DCIS [29].

Silverstein incorporated these predictors in a prognostic index called the Van Nuys Prognostic Index (USC/VNPI), designed as a scoring system to support patients and clinicians regarding the need for adjuvant RT [28]. It was suggested that patients with low USC/VNPI scores (4 to 6) could be treated with excision alone, while patients with intermediate scores (7 to 9) showed an average of 10 to 15% LR benefits with the addition of RT after BCS. Patients with high score (>10) seem to be unsuitable for BCS (as recurrences are high with or without RT) and should be considered for total mastectomy.

Unfortunately, this scoring system has never been validated by prospective studies, and some feel that although the authors demonstrate a high level of dedication and expertise in the treatment of this disease, reproducibility in clinical practice has never been demonstrated.

In an attempt to clarify this controversy and to assess the role of documented free margins and the reproducibility of Silverstein's experience, the Eastern Cooperative Oncology Group (ECOG) designed a prospective single arm study of excision alone in 671 selected patients with DCIS whose diameter was less than 2.5 cm if low-grade, or less than 1 cm if high-grade [30]. Surgical specimens were sequentially sectioned and completely embedded to determine tumor size, grade, and the margin status, stratifying patients on tumor grade and intention to administer tamoxifen. Postexcision magnification mammography was also always performed to document removal of all calcifications.

In the high-grade DCIS the rate of ipsilateral recurrence was 15.3%, suggesting excision alone is associated with a high risk of local recurrence for high-grade DCIS, even if wide (almost 3 mm) surgical margins are required. In the low-/intermediate-grade group however, the 5-year rate of ipsilateral breast events was 6.1%, a result which could be considered acceptable by many patients and physicians. Results were even more favourable for tumors less than 10 mm in diameter, or for patients >45 years of age.

However, it is well recognized that while local relapse after treatment of low-grade DCIS may take longer to present clinically compared to high-grade lesions, its incidence definitely approaches the latter group with longer follow-up [31]. Therefore, interpretation of this data necessitates caution, and more time is needed to confirm the finding of this trial.

Another prospective study on 158 patients with predominantly grade 1 or 2 lesions treated exclusively with surgery without RT [32], was recently presented by Wong et al. The protocol required a margin width of 1 cm or more. The 5-year local recurrence rate was 12%, and 31% of the recurrences were invasive, resulting in premature closure of the study.

A study of women with low-grade DCIS treated with biopsy alone from 1950 to 1968 and observed for a long period of time is not only of historical interest. Even this study showed a risk of developing invasive cancer for ipsilateral relapse in 30% of cases at 15 years [33].

Recently, a long-term follow-up evaluating invasive ipsilateral breast recurrence among participants in the two NABP trials (NSABP B17 and B24) has been published [34]. This is an important study because these two trials remain the largest prospective evaluation of breast conservation for DCIS to date. While 54% of local failures were invasive, the 15-year risk of this event was 19.4% for local excision, and 8.9% for local excision plus radiation. Compared with women aged 65 years and older, women younger than 45 years showed a 2.1-fold increase of invasive recurrences. Similarly, the margin status in NSABP B24 was associated with an approximately twofold increase of invasive recurrence. Overall, breast-cancer mortality did not differ between patients who received RT and those who did not. However, women who developed an ipsilateral invasive recurrence had a 1.75-fold greater risk of death compared with those who did not, and a 7.06-fold greater risk of breast cancer-related deaths.

Therefore, the main issue in treating DCIS is the prevention of invasive relapses, because not all of them will be curable. No doubts, our attention is directed towards the identification of subgroups of patients (e.g., those with low grade tumors, age >60, adequate margins) that could avoid RT after surgical treatment of DCIS, and in the last 2 years many reports and Consensus statements have focused on this, including the Saint Gallen Consensus Conference [35], the Newport Consensus Conference III [36], and the National Consensus Cancer Network [37].

However, from a very practical point of view, even the width of surgical margin remains controversial for the treatment of DCIS, and while the "Consensus on DCIS of Philadelphia" has proposed a 10 mm margin [38], others have proposed margins of 1 to 3 mm as adequate [39].

Another controversial issue regarding DCIS is whether patients with DCIS benefit from tamoxifen. While it is well known that women with hormone-receptor positive invasive breast cancer benefit from the addition of tamoxifen, its role on local control after excision of DCIS is not well quantified.

In NSABP-B-24 trial [13], the addition of tamoxifen resulted in a risk reduction of 16% compared with RT + placebo (HR = 0.84, 95% CI = 0.60 to 1.19, $P = 0.33$), while the UKCCCR trial [18] found a nonsignificant effect in regard of all breast events.

The different findings in these two trials may be the result of differences in the patient populations: in NSABP B-24

there was a higher proportion of young patients, ER positive, and low-grade DCIS with respect to those of UKCCCR. Furthermore, NSABP B-24 included patients with positive margins. This could in part explain the discrepancies in the outcomes between the group with tamoxifen and the group with placebo.

Therefore, the question remains of whether there are subgroups of patients for whom RT or tamoxifen is more or less effective in terms of absolute risk reduction.

Few trials were designed to clarify this important issue.

RTOG 9804 and the UK DCIS II trials are both designed to compare RT plus endocrine therapy with endocrine therapy alone for low-risk DCIS (grades 1-2 up to 3 cm with clear margins of at least 3 mm).

RTOG 9804 accrued 636 patients out of a target of 1790, and has been recently closed. The results of these trials will provide further information on the efficacy of excision alone and may allow the development of criteria to identify subgroups of patients who may not require adjuvant RT.

5. Ongoing Trials

Although many questions remain open despite the increasing interest in this disease, it is reassuring that there are many ongoing clinical trials to clarify several aspects regarding treatment of DCIS (see http://www.clinicaltrials.gov/ for further information).

The role of MRI in the diagnosis and evaluation of the extent of DCIS will be assessed in several small trials sponsored by the Memorial Sloan-Kettering Cancer Center, the University of California at San Francisco, and in Europe by the Centre Lacassagne in Nice.

Wide excision alone in grades 1-2 DCIS less than 2.5 cm in diameter is being investigated by a phase II trial sponsored by the Dana-Farber Cancer Institute. Similarly, the UK ICR-DCIS-II study is studying adjuvant RT after surgery for hormone-responsive DCIS receiving tamoxifen or anastrozole. This is a randomized trial with a target accrual of 2000 patients started in 2004.

Different radiation approaches are being investigated by several trials. Targeted intraoperative RT (20 Gy to surface of tumor bed) is being evaluated at the USC/Norris Comprehensive Cancer Center in 116 patients, and the estimated completion date is 2013. The role of a boost to the tumor bed is currently studied in a phase III multicentric trial in France, with a projected enrollment of 1950 patients. Hypofractionation is being studied by a randomized trial sponsored by MD Anderson Cancer Center comparing conventional whole-breast radiation to 42 Gy in 16 fractions and a boost of 10 Gy in 4 fractions. Estimated enrolment is 200 patients with an expected completion date by 2014.

NSABP B35 is a randomized trial, with a target of 3100 patients, comparing tamoxifen versus anastrozole in the treatment of postmenopausal women with DCIS; results will be available in 2016.

NSABP B-43 is a randomized trial investigating the role of adjuvant Trastuzumab in women after lumpectomy and RT; completion is estimated in 2019. Finally, neoadjuvat approaches, including the use of Aromatase Inhibitor in hormone-positive DCIS, and of Herceptin in neu + DCIS are currently being investigated.

6. Conclusions

Based on available evidence obtained from prospective clinical trials, patients with DCIS have potential benefit from RT after BCS with up to 60% risk reduction for ipsilateral recurrence.

However, the natural history of DCIS after surgical treatment is very variable, and the balance between benefit and risk of RT may differ in patients with low- and high-risk disease.

The ultimate goal in treating DCIS may be to accurately identify which patients can safely omit adjuvant RT because their risk of developing a potential life-threatening relapse with invasive carcinoma is low. Actually, there is no evidence from randomized or prospective trials that it is possible to define a low-risk group of patients for whom RT can be safely avoided.

Finally, although we may identify low-risk patients, the potential impact of LR after conservative treatment of DCIS, and its physical and psychological consequences must be properly and individually considered, as the ultimate goal of treatment may be different for different patients.

Many controversial issues on DCIS will probably be resolved if molecular predictors of progression and relapse to invasive carcinoma can be identified.

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Review Article

Role of the Radiotherapy Boost on Local Control in Ductal Carcinoma *In Situ*

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Ductal carcinoma *in situ* of the breast is associated with low mortality rates, but local relapse is a matter of concern in this disease. Risk factors for local relapse include young age, close or positive margins, and tumor necrosis. Whole breast irradiation following breast-conserving surgery for ductal carcinoma *in situ* significantly reduces the risk of local relapse as compared to breast-conserving surgery alone. Studies point to similar outcomes between breast-conserving surgery plus radiotherapy and mastectomy, in the absence of extensive disease. A complementary boost to the surgical bed improves outcomes for patients with invasive breast cancer. However, the effect of this strategy has never been prospectively reported for ductal carcinoma *in situ*. Two randomized controlled trials assessing this issue are ongoing. This paper represents an update on available literature about radiotherapy for DCIS with a special focus on the role of a radiotherapy boost to the tumor bed.

1. Introduction

Ductal carcinoma *in situ* (DCIS) is a proliferation of malignant cells inside galactophoric ducts without basal membrane invasion. Its incidence has dramatically increased in the recent years due to the widespread use of mammographic screening. Accounting for approximately 20 to 30% of the breast cancer cases [1], DCIS is heterogeneous in clinical presentation, varying from a palpable mass, mammographically detected tumor, or nipple discharge [2]. Despite a high cure rate, invasive recurrence and death may occur in case of insufficient local treatment. Patients with clinically large, multicentric, and extensive tumors are more likely to undergo mastectomy than breast-conserving surgery (BCS), because of a higher risk of recurrence [3]. Likewise, mastectomy may be the preferred strategy in case of diffuse suspicious-appearing microcalcifications in the breast, inability to obtain margin control by lumpectomy and/or reexcision(s), medical contraindication to irradiation, and when an unfavorable tumor-to-breast size ratio does not permit margin-negative lumpectomy with cosmetically acceptable results [4].

No randomized controlled trials comparing mastectomy with more conserving management are available, but different studies point to similar outcomes between BCS plus radiotherapy and mastectomy, whereas BCS alone tends to be inferior [5]. Therefore, BCS plus radiotherapy is an accepted strategy when mastectomy can be avoided, in view of the morbidity of radical surgery and the favorable prognosis of such patients. A number of randomized controlled trials of adjuvant radiotherapy have indeed demonstrated a reduced risk of both invasive and local recurrences, as well as a low risk of side effects [6, 7].

A radiation boost to the tumor bed has been shown to significantly improve local control in patients with invasive breast cancer [8, 9]. However, the usefulness of a boost has not been so well assessed in the setting of DCIS, and prospective studies are missing.

This paper aims at updating available literature on the subject and at developing the rationale for randomized

multicenter phase 3 studies assessing the role of surgical bed boost following whole breast irradiation (WBI).

2. Risk Factors for Local Relapse following Breast-Conserving Therapy

Several studies have attempted to identify the local recurrence risk factors following breast-conserving surgery [10]. Clinical factors have been determined by uni- and multivariate analysis of randomized trials and multicenter retrospective studies. These findings suggest that a family history of breast cancer, a young-onset disease, and a palpable tumor of more than 1 cm are factors that may adversely affect local control [11–13]. Moreover, the comedocarcinoma subtype, a histopathology size greater than 10 mm, necrosis, and positive margins have been shown to be statistically significant predictive factors for recurrence in women under 40 years old [14].

Close or positive margins are considered to be risk factors for recurrence, whether patients are irradiated or not. In the B-24 and EORTC 10853 trials, although patients were supposed to have free margins for inclusion [15, 16], a central pathology review of the specimens found a significant amount of positive and unknown margins [17]. In these trials, positive margins were found to be independent factors for the development of local relapse after BCS [18]. According to the meta-analysis of Dunne et al., a margin threshold of 2 mm may be sufficient when BCS is combined with RT [19].

Apart from margins status, tumor necrosis appears to be an important relapse risk factor, even in multifactorial analysis [20]. The histological size, the Scarff-Bloom-Richardson grade, and the degree of differentiation are minor prognostic factors. No prognostic biological or genetic factors have been individualized so far in ductal carcinoma *in situ* [21].

3. The Influence of Adjuvant Radiotherapy in the Conserving Treatment of DCIS

The role of WBI is to reduce the rate of local relapse and to allow for breast conservation. Monocenter and multicenter retrospective studies with 5 to 15 years of followup found recurrence rates of about 7 to 17%. About half of recurrences were invasive, and the metastatic rate was less than 10%. Nevertheless, these studies had heterogeneous inclusion criteria, surgical treatment, radiation dose, and followup [22].

Four randomized controlled trials have assessed the role of irradiation in this setting. A worldwide collaboration group, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), has centrally reviewed these four trials to give an updated overview of the impact of radiotherapy in DCIS. The latest report confirmed a 15.2% reduction in the absolute 10-year risk of ipsilateral breast event, regardless of age at diagnosis, extent of breast-conserving therapy, use of tamoxifen, margin status, comedonecrosis, focality, grade, or tumor size. The amount of risk reduction was higher in older women (>50 years). However, no significant effect on overall mortality or breast cancer mortality was found after a followup of 10 years [7].

3.1. NSABP B17. The NSABP B17 trial was undertaken in the United States and Canada from 1985 to 1990. The results of this trial were first published in 1993 and then updated in 2001 [23, 24]. A total of 818 patients were randomized, after initial lumpectomy for DCIS, to either surveillance or WBI to 50 Gy in 25 fractions without tumor bed boost. After a mean followup of 129 months, a 57% reduction in the risk of invasive and *in situ* breast recurrences was seen. No differences in overall survival, metastatic, or contralateral cancer rates were shown. A pooled analysis of this study and of the NSABP B24 trial confirmed a 52% reduction in ipsilateral breast recurrence risk at 15 years when patients were offered radiation therapy [25].

3.2. EORTC 10853. This trial was conducted in Europe from 1986 to 1996 and accrued one thousand and ten DCIS patients with free margins after lumpectomy. First analysis after a followup of 4.2 years showed a significant reduction in invasive relapse risk, an increased risk of contralateral cancer, and equivalent survival and metastatic rates [17]. An update after a followup of 10.5 years confirmed these results, with a 48% reduction in intraductal recurrences and a 42% decrease in invasive relapses [18].

3.3. UK/ANZ DCIS Trial. This English study was a multicenter randomized trial which assessed both the influence of WBI and the role of tamoxifen adjuvant treatment following BCS. Randomization was independent for radiotherapy and tamoxifen, stratified by screening center, and blocked in groups of four [26]. One thousand seven-hundred and one patients were accrued and one thousand and thirty patients were randomized to radiotherapy or observation. This trial has been recently updated after a followup of 12.7 years [27]. The overall reduction in local relapse was 59%, and the ipsilateral invasive disease risk reduction was 68%. No difference in the number of contralateral cancer cases was seen. The risk reduction was similar whether patients had tamoxifen or not.

3.4. SweDCIS Trial. This multicenter Swedish trial enrolled DCIS patients treated by BCS with tumor-free margins. One thousand and forty-six women were randomized to either radiotherapy or no radiotherapy. Once again, the analysis after a followup of 5.2 years showed a 3-fold reduction in invasive and *in situ* local relapses [28]. An updated analysis published in 2008 confirmed a relative risk reduction of 60% in local recurrence [29]. Women more than 50 years seemed to benefit most from adjuvant radiotherapy in this trial, and the authors concluded that older age should not preclude DCIS women from radiotherapy.

4. The Role of the Radiotherapy Boost following BCS and WBI in DCIS

The rationale for dose escalation to the tumor bed relies on the frequent presence of residual tumor cells in a 10 mm

radius of the tumor. A dose of 50 Gy does not seem to be high enough to kill such remaining cells. However, wider excisions with extensive margins significantly alter the cosmetic results. Margins greater than 2 or 3 mm are considered safe, despite a risk of remaining tumor cells of up to 20% [19, 22]. This risk legitimates dose escalation studies in DCIS.

Several retrospective studies have tried to assess the role of a boost following WBI for DCIS.

An international multicenter retrospective study was performed on 373 patients, aged 45 years or less, treated in 18 institutions [30]. Forty five percent of them underwent WBI, 40% underwent WBI plus a boost, and 15% had no radiotherapy. The relapse-free survival rates at ten years were 46% without radiotherapy, 72% in the WBI group, and 86% in the WBI plus boost group. Differences were statistically significant with an overall risk reduction for local relapse of 66% with WBI and 85% with WBI and boost. In multivariate analysis, the margins status and the radiation dose were the only two independent factors for relapse-free survival. No difference in overall survival was found.

Another study by Wong et al. confirmed the favorable effect of the radiation boost, with no local relapse observed among 79 patients receiving a boost, whereas 8 of 141 patients in the "no-boost" group experienced in-breast local recurrence [31]. These results were obtained despite a higher risk for local relapse in the boost group: 48% (boost group) *versus* 8% (no boost group) had positive or less than 1 mm margins.

On the contrary, other reports found no difference in local relapse according to the total radiation dose level: <60 Gy *versus* >60 Gy [32], <60 Gy *versus* 60–66 Gy *versus* >66 Gy [13, 33, 34]. In the study by Wai et al., only 50% of patients had radiotherapy after BCS, including 35% receiving WBI without boost and 15% receiving WBI plus a boost to the lumpectomy bed [35]. Moreover, partial breast boost was used primarily in subjects with positive or close margins, which could alter the outcome of these patients and explain these different results. If a retrospective cohort study of 208 DCIS patients with close or focally involved margins after BCS appeared to show a similar effect of a 16-Gy boost to that of a reexcision [36], prospective studies are warranted to confirm this finding before reexcision may be avoided in all cases.

5. Ongoing Clinical Trials and Future Directions

Two randomized controlled trials addressing the role of a 16 Gy boost are ongoing, and patients are currently being recruited.

An international trial of the Trans-Tasman Radiation Oncology Group, started in 2008, simultaneously evaluates the role of the boost to the tumor bed and the effect of hypofractionation on outcomes in DCIS. Patients are divided into 3 strata and randomized within those groups: group A is designed to evaluate the effect of the boost and of the fractionation schedule, group B, the boost after 50 Gy in 25 fractions of WBI, and group C assesses the interest of the boost after 42.5 Gy in 16 fractions and 22 days of WBI.

In the French multicenter prospective randomized Bonbis trial, DCIS women aged 18 and over are randomly assigned to a 16 Gy boost or no boost, following BCS and the delivery of 50 Gy in 25 fractions to the whole breast [37]. Nearly half of the patients have been enrolled so far (900 of the planned 1950 women). Inclusion criteria include tumor-free margins, the presence of surgical clips in the lumpectomy bed to ease the boost delivery, and no past history of cancer. A centralized review of all specimens is performed, as well as an assessment of dummy runs and technical radiotherapy cases. Radiotherapy should start within 12 weeks of surgery. Translational studies investigating candidate genes and a predictive test of late toxicity will hopefully help to individualize patients who can be safely treated with dose escalation to the tumor bed.

6. Summary

BCS plus WBI is an accepted strategy for DCIS when mastectomy can be avoided. The effect of a complementary boost to the tumor bed has never been prospectively assessed. Two ongoing randomized controlled trials addressing this issue should help to individualize patients who may benefit from this treatment.

Conflict of Interests

The authors declare that they have no conflict of interests.

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Research Article

Cell Polarity, Epithelial-Mesenchymal Transition, and Cell-Fate Decision Gene Expression in Ductal Carcinoma In Situ

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Loss of epithelial cell identity and acquisition of mesenchymal features are early events in the neoplastic transformation of mammary cells. We investigated the pattern of expression of a selected panel of genes associated with cell polarity and apical junction complex or involved in TGF-β-mediated epithelial-mesenchymal transition and cell-fate decision in a series of DCIS and corresponding patient-matched normal tissue. Additionally, we compared DCIS gene profile with that of atypical ductal hyperplasia (ADH) from the same patient. Statistical analysis identified a "core" of genes differentially expressed in both precursors with respect to the corresponding normal tissue mainly associated with a terminally differentiated luminal estrogen-dependent phenotype, in agreement with the model according to which ER-positive invasive breast cancer derives from ER-positive progenitor cells, and with an autocrine production of estrogens through androgens conversion. Although preliminary, present findings provide transcriptomic confirmation that, at least for the panel of genes considered in present study, ADH and DCIS are part of a tumorigenic multistep process and strongly arise the necessity for the regulation, maybe using aromatase inhibitors, of the intratumoral and/or circulating concentration of biologically active androgens in DCIS patients to timely hamper abnormal estrogens production and block estrogen-induced cell proliferation.

1. Introduction

Ductal carcinoma in situ (DCIS), also known as intraductal carcinoma, is the most common type of noninvasive breast cancer in women [1]. From the mid-1970s, the incidence of DCIS has sharply increased, primarily because of the adoption of radiographic screening for invasive carcinoma. Currently, it accounts for approximately 25% of newly diagnosed breast cancer cases [1].

DCIS is a nonobligate precursor to invasive breast cancer, and for this reason some members of the 2009 US National Institutes of Health DCIS consensus conference proposed to remove the word "carcinoma" from the term DCIS [2]. Nevertheless, experimental studies have shown the presence of carcinoma precursor cells in DCIS lesions [3–5], and clinical evidence indicates that approximately 50% of cases will progress to invasive breast cancer if untreated [6, 7]. As a result, the malignant nature of DCIS remains debated, primarily because of the limited knowledge of DCIS arising and development. In fact, while several genome-wide studies have compared the gene profiles of DCIS and invasive breast cancer, very few studies have investigated and recognized the molecular alteration that characterize DCIS with respect to normal tissue [8–11].

DCIS is defined as an abnormal proliferation of transformed mammary epithelial cells within the closed environment of a duct, likely in response to microenvironment alterations including hypoxia and nutrient deprivation [4, 12]. Among the processes early affected during mammary cells transformation, those involved in the establishment and maintenance of epithelial cell identity and tissue specificity are of particular relevance. In fact, epithelial mammary cells are characterized by an asymmetric distribution of cytoplasmic and membrane proteins, termed apicobasolateral cell

polarity, essential for a correct cell-cell adhesion and the formation of an epithelial sheet. As a result of an epithelial to mesenchymal transition (EMT), during neoplastic transformation, cell polarity and epithelial morphology are early lost polarized and immotile epithelial cells acquire a fibroblast-like morphology and increased cell motility [13].

EMT process can be induced by a variety of signaling pathways among which the main and best characterized is that involving transforming-growth factor-β (TGF-β). TGF-β is a multifunctional cytokine and a powerful tumor suppressor that governs many aspects of mammary epithelial cells physiology and homeostasis [14]. Under abnormal microenvironment conditions; however, some mammary epithelial cells may acquire resistance to TGF-β, circumvent its cytostatic effect and tumor suppressive activity, and activate EMT [15, 16].

Recent studies have demonstrated that EMT may generate cells with stemness-like properties, especially in the transitioning mammary epithelial cell compartment [17, 18]. Therefore, a interrelationship among EMT (TGF-β mediated), disruption of the mechanisms deputed to cell polarity and adhesion control, and acquisition of stemness-like features can be assumed already in DCIS [19, 20].

Taking advantage from the only microarray dataset publicly accessible at the ArrayExpress web site, we investigated the pattern of expression of a selected panel of genes involved in TGF-β-mediated EMT or associated with epithelial cells identity (i.e., cell polarity and apical junction complex) and cell-fate decision in a series of DCIS and corresponding patient-matched histologically normal (HN) epithelium [11]. As the whole-gene expression profile of patient-matched atypical ductal hyperplasia (ADH) was also available, we further compared DCIS and ADH profiles to verify the hypothesis according to which breast cancer progression is a multistep process involving a continuum of changes from normal phenotype through hyperplastic lesions, carcinoma in situ, and invasive carcinoma [21].

2. Materials and Methods

2.1. Materials. As reported in the original paper [11], patient-matched samples (HN, ADH, and DCIS) were isolated via laser capture microdissection from surgical specimens of 12 preoperative untreated patients with an ER-positive (immunohistochemically evaluated) sporadic breast cancer. Gene expression was determined by using the Affymetrix Human Genome HG-U133A GeneChip; corresponding microarray dataset was publicly available at the ArrayExpress web site (http://www.ebi.ac.uk/arrayexpress/) with the Accession number E-GEOD-16873.

2.2. Gene Selection. To select the panel of genes specifically involved in the TGF-β-activated EMT, cell polarity and apical junction complex, and cell-fate decision, we combined Gene Ontology (http://www.geneontology.org) and PubMed (http://www.ncbi.nlm.nih.gov) information. In addition, since cancer cells often increase their autocrine production of TGF-β to activate angiogenesis in response to oxygen and nutrients deprivation [14], we also included some genes coding for angiogenesis-inducing factors. On the whole, a set of 199 genes evolutionarily conserved in *Homo sapiens* was established (see Supplementary Table 1 available on line at doi 10.1155/2012/984346). However, because 27 genes had no corresponding probe-sets on the HG-U133A GeneChip, the gene set was actually composed of 172 elements, 33 of which involved in EMT activation [13–15, 21–23], 75 involved in cell polarity and apical junction assembly [24–26], 36 involved in cell fate-decisions and in the maintenance of a self-renewal state in tumorigenic adult tissues [27–29], 28 involved in hormone steroid signaling [30–32], angiogenesis activation [33, 34] or used as luminal and basal markers [35–38]. These 172 genes corresponded to 339 Affymetrix probe-sets, as verified by GeneAnnot system v2.0 (http://bioinfo2.weizmann.ac.il/geneannot/), that additionally provided us information about the quality of each probe-set in terms of sensitivity and specificity score [39] (see Supplementary Table 2).

2.3. Statistical Analysis. As some genes are recognized by more than a single probe set, each of which characterized by an individual specificity and sensitivity that differently contribute to gene expression value, a gene expression mean value was calculated after weighting each probe-set for its own sensitivity and specificity score. Specifically, each expression value (already log 2 transformed in the original dataset) was multiplied for the semi sum of sensitivity and specificity scores of the corresponding probe set. Given the patient-matched samples study design, all statistical analyses were performed considering a regression model for repeated measures with random effect, and the differential gene expression was evaluated by t-test on regression coefficients. To correct for multiple testing, the false discovery rate (FDR) was used [40].

To evidence latent variables accounting for genes correlations, a factor analysis was applied [41] in the following three comparisons: DCIS and paired ADH, DCIS and paired HN, and ADH and paired HN. The number of retained factors was selected according to the scree test [42]. To facilitate the interpretation of the factors, varimax rotation was applied. Loading values lower than 0.3 were not considered.

All analyses were performed using open source software R 2.11.1 packages HDMD (http://www.R-project.org).

3. Results and Discussion

Genes found differentially expressed ($P < 0.05$) between DCIS and NH or ADH and NH are reported in Table 1. Specifically, 47 of the 172 selected genes were found differentially expressed between DCIS and NH (11 with an estimated FDR < 0.01) and 28 were found differentially expressed between ADH and NH (only one with an estimated FDR < 0.01). Notably, 24 of the 28 genes found differentially expressed between ADH and NH were found differentially ex-pressed (in a similar manner) also between DCIS and NH. The persistence of this "core" of genes, dysregulated in a similar manner in both invasive breast cancer precursors,

Table 1: Differentially expressed genes between ADH or DCIS and histologically normal (HN) tissue (ordered according to *P* value).

ADH versus HN			DCIS versus HN		
Gene symbol	*P* value	Variation	Gene symbol	*P* value	Variation
JAM3	0.000045	↓	**JAM3**	0.000016	↓
JAG2	0.000337	↓	**EGFR**	0.000103	↓
CD24	0.000364	↑	**SNAI2**	0.000127	↓
SNAI2	0.000594	↓	**CLDN5**	0.000136	↓
EGFR	0.001897	↓	**JAM2**	0.000150	↓
FOXC1	0.002222	↓	**FOXC1**	0.000167	↓
EGF	0.003163	↓	**CD24**	0.000277	↑
ID2	0.003547	↑	**JAG2**	0.000297	↓
JAM2	0.005052	↓	**KRT5**	0.000420	↓
TJP3	0.005070	↑	**KRT14**	0.000425	↓
TGFBR3	0.005537	↓	**GATA3**	0.000490	↑
KRT17	0.005624	↓	TGFBR3	0.000710	↓
GATA3	0.005795	↑	TJP3	0.001046	↑
TP53	0.006737	↑	KRT17	0.001402	↓
CDH4	0.006916	↓	SOX4	0.001942	↑
AKT1	0.009044	↑	AKT1	0.002867	↑
CLDN7	0.012026	↑	CLDN8	0.003090	↓
EPCAM	0.015207	↑	CDC42	0.003643	↑
ABCG2	0.019210	↓	EGF	0.003752	↓
KRT5	0.019854	↓	EPCAM	0.004605	↑
KRT14	0.020117	↓	CLDN7	0.004749	↑
CLDN11	0.023005	↓	ESR1	0.007188	↑
PARD3	0.030202	↓	DLG1	0.007249	↑
SOX4	0.036127	↑	KRT19	0.007637	↑
CDC42	0.036404	↑	FOXA1	0.007844	↑
TIAM1	0.038034	↑	KRT18	0.010091	↑
ESR1	0.038527	↑	CDH3	0.010638	↓
PVR	0.039104	↓	TIAM1	0.010722	↑
			TGFBR2	0.013243	↓
			RHOA	0.013540	↑
			BRCA1	0.014098	↑
			ID4	0.017030	↓
			ID2	0.018115	↑
			NOTCH4	0.018550	↓
			PVRL2	0.019914	↑
			AKT3	0.020275	↓
			ACTN1	0.020619	↓
			PROM1	0.022238	↓
			CDH4	0.022933	↓
			DLG3	0.023798	↑
			F11R	0.031657	↑
			CTNNA1	0.033234	↑
			MTA2	0.033999	↓
			ABCG2	0.037966	↓
			MPP5	0.039023	↑
			HIF1A	0.039489	↑
			CDKN1A	0.047769	↑

In bold, genes with an estimated FDR < 0.01.

seems to support the hypothesis of ADH as the direct precursor of DCIS. In fact, in agreement with the proposed multistep process, DCIS showed an increased number of genes differentially expressed with respect to ADH.

With respect to normal tissue, both DCIS and ADH showed the overexpression of *ESR1*, coding for the estrogen receptor; *CD24,* coding for a mucin-like cell-adhesion molecule positively associated with a terminally differentiated luminal phenotype [43, 44]; *GATA3,* coding for a transcription factor involved in mammary gland morphogenesis [35, 36]; *CLDN7*, *EPCAM,* and *TJP3*, coding for tight junction components; *CDC42* and *TIAM1*, coding for two small GTPase family members involved in cell polarity and apical junction complex formation. Concomitantly, both breast cancer precursors showed the underexpression of *EGFR* gene, in which expression is generally negatively associated with *ESR1* expression, *KRT5*, *KRT14,* and *KRT17*, all coding for cytokeratins associated with a basal phenotype. On the whole, this pattern of expression clearly indicates that DCIS and ADH are both characterized by a terminally differentiated luminal phenotype. Since all specimens were derived from patients with an ER-positive ductal carcinoma, it is conceivable the hypothesis that the establishment of an estrogen-dependent phenotype, in response to estrogens present in the microenvironment, should be a very early event in the tumorigenic process. Such a finding is in agreement with the model for breast cancer development proposed by Dontu et al. [45], according to which ER-positive cancers should derive from transiently amplifying ERpositive progenitor cells. Escaped from proliferation control as a consequence of genetic and epigenetic alterations in genes involved in cell-fate decision, these ER-positive progenitor cells should generate cells constitutively expressing estrogen receptor. Once established in ADH, this terminally differentiated luminal phenotype seems to consolidate in DCIS as demonstrated by the presence, among the genes exclusively expressed in DCIS, of *KRT18, KRT19* (coding for some luminal-associated cytokeratins) and *DLG1, DLG3,* and *MPP5* (coding for some cell polarity complex components).

With respect to both tumor precursors, histologically normal tissue expressed genes coding for some transcription factors involved in EMT (*SNAI2* and *TGFBR3*) and cell-fate decision (*FOXC1* and *JAG2),* and for stemness-associated features (*ABCG2*). This finding is more evident considering the 47 genes differentially expressed between DCIS and normal tissue among which we found some other genes involved in the TGF-β-mediated EMT (*AKT3, ID4* and *TGFBR2*), and cell-fate decision and self-renewal (*NOTCH4* and *PROM1*).

Such an apparently paradoxical finding, that is, the positive association between histologically normal tissues and EMT- and stemness-related genes (more likely expected in transformed tissues) is not surprising since we observed a similar behavior in an independent cases series composed of primary breast cancers and corresponding patient-matched normal tissue (submitted paper) and in normal pleura with respect to pleural mesothelioma [46]. In agreement with the physiological remodeling of the mammary gland, such a finding should support the persistence of resident stem/progenitor cells in normal tissue [47, 48].

Factor analysis, applied to investigate the latent variables intrinsically associated with the selected 172 genes, corroborated these findings and highlighted some other interesting interrelations. In agreement with the results provided by *t*-paired test, factor analysis indicated that in both precursors (Figure 1(a) for DCIS and Figure 2(a) for ADH), the first factor (F1) was principally characterized by genes associated with an estrogen-dependent epithelial phenotype. In fact, within the genes with a positive loading value on F1, we found those coding for hormone steroid receptors (*AR* and *ESR1*) and transcriptional coactivator for steroid and nuclear hormone receptors (*NCOA1*), for tight (*EPCAM, MAGI1, MAGI2, MPDZ, TJP1, TJP2* and *TJP3*) and adherens (*CTNND1, PFN1* and *PVRL2*) junction components, and for small GTPase family members involved in epithelial cell polarization processes (*CDC42* and *RHOA*). In addition, we found some genes associated with cell-fate decision: *BMI-1,* coding for a member of Polycomb group required to maintain the transcriptionally repressive state of many genes throughout embryo development [49] and adult tissues differentiation including mammary gland [50]; *FDZ4* and *FDZ6*, two members of the frizzled gene family involved in β-catenin-signaling transduction and intercellular transmission of polarity information in differentiated tissues [51].

Furthermore, in agreement with the notion that ERα, and TGF-β-signaling pathways are major regulators during mammary gland development [52], we found genes coding for TGF-β receptor *(TGFBR3)* or for proteins involved in canonical (*ID1, SMAD2* and *SMAD4*) and noncanonical (*PTEN*, *RHOA* and *ROCK1*) TGF-β pathways [15, 16].

Finally, probably associated with the adaptation of DCIS and ADH to hypoxic stress caused by the unbalance between cell proliferation and oxygen supply, we also found *JAM2, JAM3, VEGFA*, *VEGFB,* and *VEGFC,* all genes involved in endothelial cell proliferation.

The second factor (F2) identified by factor analysis (Figure 1(b) for DCIS and Figure 2(b) for ADH) was conversely characterized by the positive loading value of several genes coding for mesenchymal markers (*EGF, EGFR, KRT5, KRT6B, KRT14* and *KRT17*), and the negative loading value of *GATA3,* the gene coding for the transcription factor driving the luminal morphogenesis of the mammary gland [35, 36]. In addition, F2 was characterized by the presence of some genes coding for proteins playing a critical role in cell-fate decision and cell-renewal (*ALDH1A3, FOXC1, NOTCH2, PROM1,* and *SOX9*) [53].

Notably, when applied to ADH subgroup, factor analysis identified *CYP19A1* as included in the panel of genes characterizing the first factor. This gene encodes for cytochrome P450 (better known as aromatase), the enzyme that catalyzes the conversion from circulating and rostenedione to estrone or testosterone to estradiol, and its presence should support the hypothesis of a very early activation of an autocrine production of estrogen. Furthermore, the concomitant presence of *CYP19A1, AR*, *ESR1,* and *NCOA1* should provide a transcriptomic confirmation for the clinical evidence that high androgens level may have detrimental effect on breast

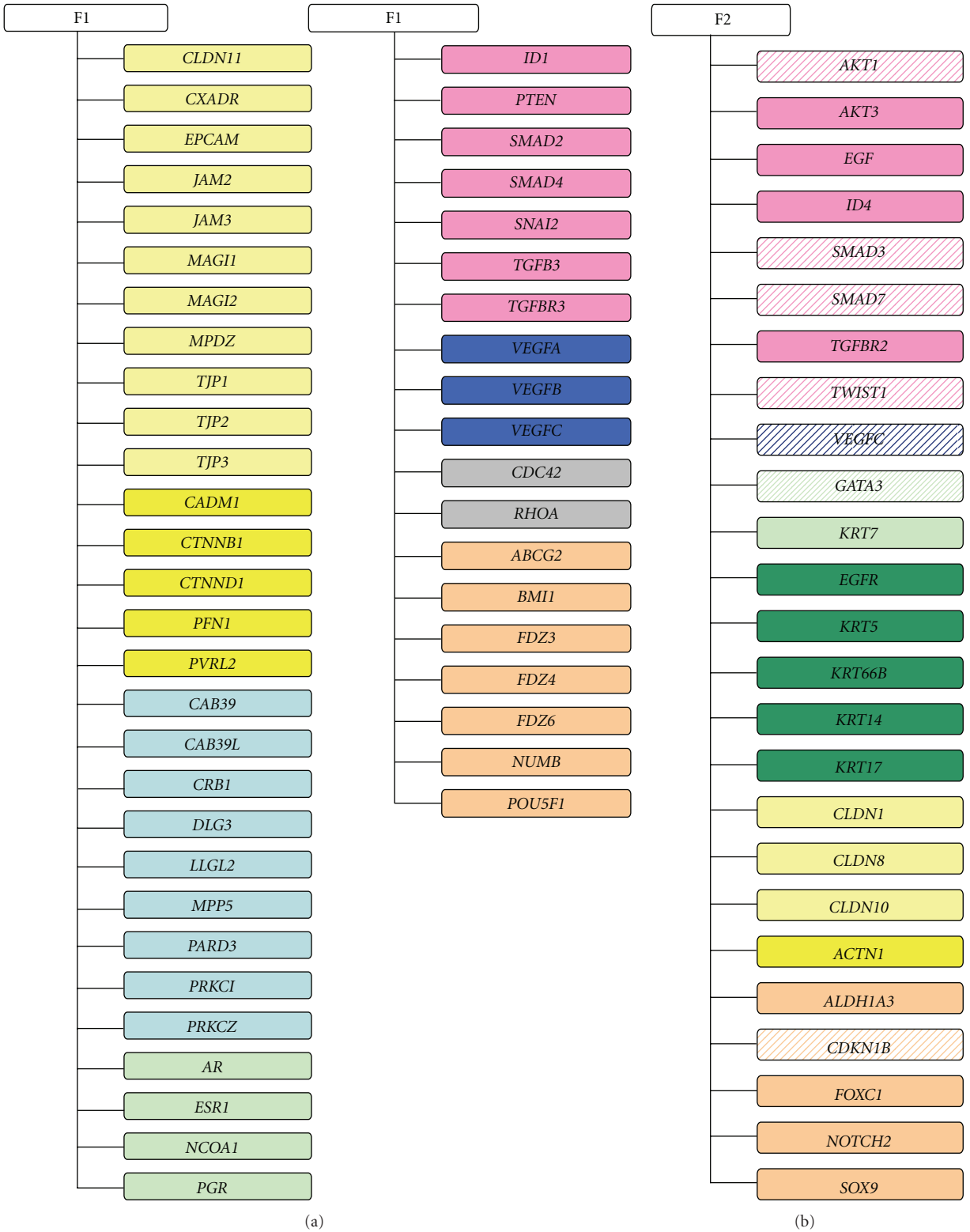

Figure 1: Factor analysis in DCIS subgroup. Schematic representation of genes with a loading value $< |0.6|$ characterizing the first (F1) and the second factor (F2). Solid color indicates a positive loading value whereas dashed color indicates a negative loading value. Color correspondence: *light yellow*, tight junction components; *dark yellow*, adherens junction components; *light blue*, polarity complexes components; *dark blue*, angiogenesis; *orange*, cell-fate decision; *light green*, luminal markers and hormone steroid; *dark green*, basal markers; *pink*, epithelial-mesenchymal transition, *grey*, GTPase family members.

Figure 2: Factor analysis in ADH subgroup. Schematic representation of genes with a loading value $< |0.6|$ characterizing the first (F1) and the second factor (F2). Solid color indicates a positive loading value whereas dashed color indicates a negative loading value. Color correspondence: *light yellow*, tight junction components; *dark yellow*, adherens junction components; *light blue*, polarity complexes components; *dark blue*, angiogenesis; *orange*, cell-fate decision; *light green*, luminal markers and hormone steroid; *dark green*, basal markers; *pink*, epithelial-mesenchymal transition, *grey*, GTPase family members.

carcinogenesis and progression due to a persistent local estrogen production that incessantly stimulates epithelial cell proliferation [54–56].

When applied to DCIS subgroup, factor analysis seems to indicate a consolidation of such an estrogen dependence as suggested by the additional presence of *PGR*, the gene coding for progesterone receptor and which expression is under estrogenic control.

4. Conclusions

Elucidating the initial steps of breast tumorigenesis is of paramount importance to allow an even early diagnosis and consequently an adequate treatment strategy aimed to prevent the malignant transformation of preneoplastic alterations. That is of particular importance for DCIS because of its high incidence [1] and facility in progressing to invasive breast cancer if untreated [6, 7].

Experimental evidence till now accumulated has clearly indicated that at the basis of the neoplastic transformation of mammary epithelial cells there are loss of apicobasal epithelial cell identity and acquisition of a functional mesenchymal morphology. Therefore, we investigated the pattern of expression of a selected panel of genes associated with epithelial cells identity (i.e., cell polarity and apical junction complex) or involved in TGF-β-mediated EMT and cell-fate decision in a series of DCIS and corresponding patient-matched normal tissue. In addition, we compared DCIS profile with that of patient-matched ADH to investigate the hypothesis according to which breast cancer progression is a multistep process involving a continuum of changes from normal phenotype through hyperplastic lesions, carcinoma in situ, and invasive carcinoma [21].

Statistical analysis seems to support this hypothesis because it identified a "core" of genes, mainly associated with a terminally differentiated luminal phenotype, and differentially expressed in both precursors with respect to the corresponding normal tissue. Notably, these alterations in gene expression did not result in a progressive mesenchymal transition but rather in a terminally differentiated luminal phenotype, in agreement with the model according to which ER-positive invasive breast cancer derives from ER-positive progenitor cells [45]. The constitutive expression of ER should make ADH and DCIS forming cells able to exploit the proliferative stimulus induced by estrogens whereas the establishment of an autocrine production of estrogens, through androgens conversion, should provide an additional selective advantage. The detrimental effect of such continuous estrogen stimulation should be corroborated by the observation that all patients included in the present study developed an invasive ER-positive ductal carcinoma.

Experimental evidence supporting the hypothesis that androgens conversion may be involved in DCIS development, and progression has been provided by a recent study in which the intratumoral concentration of estradiol and 5α-dihydrotestosterone (DHT), and the expression of some sex steroid-producing enzymes, including aromatase, has been evaluated in DCIS specimens [57]. The study clearly demonstrated that aromatase expression level was significantly higher in DCIS with respect to nonneoplastic tissue suggesting the self-sustaining process adopted by DCIS.

Taken together all these findings provide transcriptomic confirmation that, at least for the panel of genes considered in present study, ADH and DCIS are part of a tumorigenic multistep process and strongly arise the necessity for the regulation, maybe using aromatase inhibitors, of the intratumoral and/or circulating concentration of biologically active androgens in DCIS patients to timely hamper abnormal estrogens production and block estrogen-induced cell proliferation [58].

There is no doubt that present *in silico* study suffers for the limitation common to the majority of studies involving gene expression profile, that is, the lack of validation, at protein level, of the modulations observed at mRNA level. In fact, it is well known that mRNA transcript levels do not always reflect protein expression. However, the immunohistochemical data provided in The Human Protein Atlas largely confirms the differential gene expression that we observed between histologically normal and cancerous tissue. For instance, when we considered the 11 genes with an estimated FDR < 0.01 (Table 1, in bold), we found that protein expression of normal breast (glandular cell) and breast cancer tissue mainly paralleled the mRNA differential expression we observed in our dataset, making our preliminary findings more reliable and worthy of further investigation.

Author's Contribution

D. Coradini and P. Boracchi contributed equally to this paper.

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Research Article

Mammary Ductal Carcinoma In Situ: A Fresh Look at Architectural Patterns

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Mammary ductal carcinoma in-situ (DCIS), a malignant appearing lesion on cytological and histological grounds, is in fact a non-obligate precancer. DCIS is difficult to manage and is sometimes treated more aggressively than invasive carcinoma. Although most DCIS classifications take into account the architectural growth pattern, when it comes to architecture, the literature is full of contradictory information. We examined 289 breast cancers and found DCIS in 265 of the cases. The majority of the DCIS cases were seen in the setting of invasive cancer and only 9% of the cases represented pure DCIS with no invasive cancer. The DCIS commonly displayed a mixed pattern with micropapillary, cribriform and solid components with the micropapillary type being the rarest, occurring seldom on its own. A continuum of growth with a micropapillary pattern evolving into a cribriform type could be seen in some of the cases. This may explain some of the conflicting information, in the literature, regarding the different architectural types of DCIS. The comedo-pattern of necrosis could be seen in all types of DCIS. We therefore conclude that the study of the determinants of growth pattern in DCIS would be the key to unravelling the diverse, often non-concordant evidence one encounters in the literature.

1. Introduction

Classifying and managing DCIS has always been a thorny issue, often dividing various groups of pathologists around the world [1].

Amongst DCIS features, the architectural pattern, its prognostic value, and role in grading DCIS have also been stirring sufficient controversy. The current literature on the subject accepts the existence of 3 major architectural patterns of DCIS, namely, the solid, cribriform, and micropapillary patterns [2].

The clinging or flat type is not universally accepted as fully developed DCIS. It has been variably considered as an early micropapillary DCIS or even a subvariant of the atypical ductal hyperplasia [3].

Other special types of DCIS, such as the apocrine, the endocrine (argyrophilic), and signet ring DCIS, are all defined on histological criteria, rather than architectural pattern and they actually belong to the solid pattern of growth.

With respect to grading, it is universally accepted that the nuclear grade is the essential feature, recurring in all classification systems previously proposed and currently in use [4].

An association, albeit inconsistent, exists between the nuclear grade and the architectural growth pattern. It is generally accepted that most micropapillary and cribriform in situ carcinomas are of low nuclear grade and relatively indolent [5]. However, in a recent publication by Fisher and colleagues, micropapillary DCIS was found to be associated with both ipsilateral and contralateral recurrence of malignancy in a statistically significant number of cases [6].

As this result appears somewhat puzzling in the light of our present knowledge and understanding of DCIS, we decided to have a new, fresh look at all cases of DCIS reported during the past approximately 10 years at the Department of

Pathology of the Royal Darwin Hospital, NT, Australia and report our findings.

2. Materials and Methods

All cases of DCIS reported at the Royal Darwin Hospital, Northern Territory, Australia between January 2001 and September 2010, representing 60% of all breast cancers in the NT were retrospectively reviewed. In order to capture all the cases, including those that may have been incorrectly coded, we verified all breast tissue reports and then selected for active review all cases of DCIS. The architectural and cytological aspects of DCIS were assessed. The presence or absence of necrosis was also evaluated.

2.1. Architecture. The 3 main types of DCIS, according to the architectural growth pattern (micropapillary, cribriform, and solid) were assessed. Architecturally DCIS was divided into single, when >90% of the in situ tumour displayed one architectural pattern, and mixed when the dominant pattern constituted <90% of the in situ carcinoma.

2.2. Nuclear Grade. Nuclear grading is based on the size of malignant cells nuclei in comparison to normal ductal epithelial cells. Grade 1 is applied when the nuclei of the malignant cell are between 1.5 and 2 times that of normal ductal epithelial cell. Grade 2 is applied when the nuclei of the malignant cell are between 2 and 2.5 times that of normal ductal epithelial cell. Grade 3 is applied when the nuclei of the malignant cell are greater than 2.5 times that of normal ductal epithelial cell [7].

2.3. Necrosis. Any necrosis in DCIS was recorded. Minimal necrosis was labelled as necrosis, not otherwise specified. The term comedonecrosis, which is poorly defined in the literature, was applied when significant necrosis, creating an appearance similar the comedos, seen in cutaneous acne, was noted in ducts with DCIS.

3. Results

A total of 289 breast carcinomas had been received at the Royal Darwin Hospital during the period of the study. These consisted of 265 invasive and 24 pure in situ cancers.

These cancers consisted of 231 infiltrating duct carcinomas of no special type, 24 infiltrating lobular carcinomas and 10 carcinomas of special type. Of these special breast cancers, 5 were pure mucinous carcinomas, 2 were invasive papillary carcinomas, 2 were tubular carcinomas, and 1 was medullary carcinoma.

DCIS was present in 133/265 (50.18%) of the invasive ductal carcinomas. The proportion of invasive ductal carcinomas containing DCIS varied from year to year, ranging from 16/26 (62%) in 2002 to 8/26 (31%) in 2007. The reason for this variation is not clear.

3.1. DCIS Subtypes. Table 1 also shows the frequency of pure DCIS and DCIS associated with invasive cancer.

Table 1: DCIS pure and with invasive cancer and growth pattern.

DCIS growth pattern (157 cases)	
Single	91 (58%)
Mixed	66 (42%)
DCIS with a single growth pattern (91 cases)	
Micropapillary	4 (5%)
Cribriform	23 (25%)
Solid	61 (67%)
Macropapillary/encysted papillary	3 (3%)
DCIS with a mixed growth pattern (66 cases)	
Micropapillary, cribriform, and solid	11 (17%)
Micropapillary and cribriform	14 (21%)
Micropapillary and solid	11 (17%)
Cribriform and solid	30 (45%)

Table 2: DCIS by growth pattern.

Micropapillary (40 cases)	
Pure micropapillary DCIS without cancer	0
Pure micropapillary DCIS with invasive cancer	4
Cribriform (78 cases)	
Pure cribriform DCIS without cancer	2
Pure cribriform DCIS with invasive cancer	21
Solid (113 cases)	
Pure solid DCIS without cancer	7
Pure solid DCIS with invasive cancer	54
Mixed DCIS (66 cases)	
Mixed DCIS without cancer	12
Mixed DCIS with invasive cancer	54
Macropapillary (3 cases)	
Pure macropapillary DCIS without cancer	3
Pure macropapillary DCIS with invasive cancer	0

Of the 157 cases of DCIS (pure DCIS and invasive cancers with DCIS), 91 (58%) displayed a single growth pattern and 66 (42%) showed a mixed growth pattern (Table 1).

Of the 91 cases of DCIS with a single growth pattern, 4 (5%) were micropapillary, 23 (25%) were cribriform, 61 (67%) were solid, and 3 (3%) were encysted papillary (Table 1).

Of the 66 mixed type DCIS cases, all 3 growth patterns (micropapillary, cribriform, and solid) were noted in 11 (17%) of the cases. Micropapillary and cribriform was present in 14 (21%), micropapillary and solid was seen in 11 (17%), and cribriform and solid was identified in 30 (45%) of the cases (Table 1).

Most of the pure in situ carcinomas were of the mixed type and there were no cases of single pattern micropapillary DCIS (Table 2).

Overall, a micropapillary pattern was seen in 40/157 (25%), a cribriform component in 78/157 (50%), a solid component in 113/157 (72%), and macropapillary (encysted papillary carcinoma) in 3 (1.9%) of the DCIS cases (Table 2).

Table 3: DCIS by nuclear grade.

All cases with any micropapillary DCIS component (40 cases)	
Low grade	2 (5%)
Intermediate grade	18 (45%)
High grade	20 (50%)
All cases with any cribriform DCIS component (78 cases)	
Low grade	17 (22%)
Intermediate grade	39 (50%)
High grade	22 (28%)
All cases with any solid DCIS component (113 cases)	
Low grade	8 (7%)
Intermediate grade	47 (42%)
High grade	58 (51%)
All cases with any mixed DCIS component (66cases)	
Low grade	8 (12%)
Intermediate grade	30 (45%)
High grade	28 (43%)
Macropapillary (3 cases)	
Low grade	3 (100%)
Intermediate grade	0 (0%)
High grade	0 (0%)

3.2. Comedonecrosis. Comedonecrosis was present in 18/40 (45%) of the micropapillary, 67/113 (59%) of the solid, and 20/78 (26%) of the cribriform cases of DCIS. These findings show that comedonecrosis is more likely to be seen in micropapillary and solid types DCIS than in the cribriform type. This association is statistically significant with P values of 0.033 and 0.00004, respectively. At the same time, no statistically significant difference in comedonecrosis occurrence was noted between the micropapillary and solid DCIS ($P = 0.117$).

3.3. Nuclear Grade. Of the 157 cases of DCIS high nuclear grade was recognised in 70 (45%), intermediate nuclear grade in 65 (41%), and low nuclear grade in 22 (14%) of the cases (Table 3).

3.4. Nuclear Grade versus Architectural Type of DCIS. Of the 40 cases of micropapillary DCIS, 2 (5%) were low grade, 18 (45%) were intermediate grade, and 20 (50%) were high grade (Table 3).

Of the 78 cases of cribriform DCIS, 17 (22%) were low grade, 39 (50%) were intermediate grade, and 22 (28%) were high grade (Table 3).

Of the 113 cases of solid DCIS, 8 (7%) were low grade, 47 (42%) were intermediate grade, and 58 (51%) were high grade (Table 3).

These results show a statistically significant difference between the presence of high nuclear grade (grade 3) in the solid and micropapillary types of DCIS compared to the cribriform type ($P = 0.0008$, and $P = 0.019$ resp.). On the other hand, no statistically significant nuclear grade differences were noted between the micropapillary and solid types ($P = 0.884$).

All three cases of macropapillary (encysted papillary carcinoma) were low grade (Table 3).

3.5. Micropapillary DCIS. Overall, we identified 40 cases with a micropapillary DCIS component (Table 2). Thirty-six of these were mixed with other growth patterns and 4 had only micropapillary growth pattern. In the cases of DCIS with no invasive cancer, there was a micropapillary component in 9 cases; all mixed with other growth patterns. The remaining 31 cases of micropapillary DCIS had an associated invasive component. Of these, 4 had only a micropapillary growth and in 27 the micropapillary pattern was mixed with other growth patterns.

Of all the 91 cases of DCIS with a single growth pattern, 4 (4%) had only micropapillary growth (Table 1). Of the 24 cases of pure DCIS, none was only micropapillary but 9 had a micropapillary component, mixed with other architectural patterns. Of these, 6 cases were high grade, 2 cases were intermediate grade, and 1 case was low grade (Table 3).

The age of patients who had a micropapillary component ranged from 38 years to 88 years with a median of 50 years. The age range for the low grade was 52 years to 63 years, for the intermediate grade was 38 years to 88 years, and for the high grade was 40 years to 80 years.

The invasive component of cases that included a micropapillary type DCIS was grade 3 in 22.6% (7/31), grade 2 in 38.7% (12/31), and grade 1 in 38.7% (12/31) of the cases.

Of the 4 cases with micropapillary DCIS not associated with any other type of DCIS (pure micropapillary type), 3 were intermediate grade and 1 was low grade. There were no high grade cases (Table 3).

The micropapillary DCIS represented only a minor component (<25%) in 9/36 of the cases in which it appeared in combination with the other types of DCIS.

3.6. Concordance between the Original Assessment and the Current Review. The cases had been reported by 6 pathologists, of which three were responsible for reporting 94% of cases. The overall concordance for all cases of DCIS, in respect to nuclear grade, regardless of architectural pattern, was very good, with a Kappa score of 0.87.

In cases with micropapillary component there was a good concordance between our evaluation and the initial report with a Kappa score of 0.61. The nonconcordant cases, which differed by 1 grade, were all between low to intermediate grade; none involved a high grade.

The concordance rate for cases not including a micropapillary pattern was also very good with a Kappa score of 0.88.

4. Discussion

It is beyond the scope of this study to chronologically recapitulate all aspects of this complex histopathological entity.

Regarding the micropapillary DCIS, our results are surprising, but may explain partly the increased correlation with breast carcinoma recurrence identified by Fisher et al. [6].

Fisher and colleagues reviewing DCIS from 1456 patients enrolled in the National Surgical Adjuvant Breast and Bowel Project (NSABP) protocol B-24 to determine predictors for ipsilateral breast tumour recurrences and contralateral breast cancers, after a median follow-up time of 10.5 years, found ductal comedonecrosis, micropapillary histological tumour type to be independent high risk factors for ipsilateral breast tumour recurrence and for contralateral breast cancers [6].

In a recent article, Castellano et al. have shown the nuclear grade to be crucial in determining the biology of micropapillary DCIS. They also showed that high nuclear grade micropapillary DCIS more frequently overexpressed HER2, showed a higher proliferation index, and displayed necrosis and microinvasion. Logistic regression analysis confirmed high nuclear grade (odds ratio, 6.86; confidence interval, 1.40–33.57) as the only parameter associated with elevated risk of local recurrence after breast-conserving surgery. However, the recurrence rate of 19 micropapillary DCIS, which were part of a cohort of 338 consecutive DCIS, was significantly higher (log-rank test, $P = 0.019$) than that of nonmicropapillary, independent of nuclear grade. The authors concluded that although nuclear grade may significantly influence the biological behaviour of micropapillary ductal carcinoma in situ, micropapillary growth pattern represents a risk factor for local recurrence after breast-conserving surgery [8].

The micropapillary pattern of DCIS is by far the rarest one in our study. It was seldom seen on its own. While the number of cases in which the micropapillary growth pattern constitutes the only pattern was very small in our study, it may not be a coincidence that none of these cases was high nuclear grade and none was associated with necrosis. This finding would be consistent with the dogma defining micropapillary DCIS as a predominantly low grade DCIS.

The frequent association between micropapillary DCIS and necrosis may explain why authors, considering comedonecrosis a separate pattern of DCIS, have been discarding all those cases also displaying comedonecrosis from the micropapillary group [8].

Another notion on which all publications seem to agree is the fact that the solid variant tends to be associated with high grade DCIS, whereas the micropapillary and cribriform variants most often form a low grade DCIS [5].

We believe comedocarcinoma is not a separate type of DCIS and should not be used as such. In other words, each DCIS should be given an architectural pattern label and the presence or absence of necrosis should be described separately.

In all the cases of DCIS with a pure micropapillary growth pattern, the nuclear grade was low or intermediate. This may mean that those cases of low grade DCIS that may have a certain genetic makeup will maintain an indolent course, whereas the more aggressive ones will undergo the changes described above and assume a mixed growth pattern with comedonecrosis.

Because of this supposed evolution, the micropapillary component may represent a minor proportion of the entire DCIS at the time the tissue is removed for histological evaluation.

If comedocarcinoma is considered a separate type of DCIS in which the architectural pattern is neglected and not reported, then our results, with only 4 cases of micropapillary DCIS, are all in keeping with the old dogma that micropapillary DCIS is a low or intermediate grade with no necrosis.

We agree with Fisher and colleagues [6] in considering comedocarcinoma a separate feature, rather than a histological type.

Pinder and O'Malley [9] hit the nail on the head and explain that comedonecrosis may be seen in association with any DCIS architectural type, and that it is not a type itself, as it is "neither a grade nor an architectur." So they clearly recommend that the term comedo-type DCIS should not be used as a characterisation of growth pattern. This is exactly what we feel and what our study supports.

Also in keeping with our view is the fact that the rare, special type DCIS, namely, the signet ring, endocrine, and other types, also have a growth pattern that is, the solid one, even if the cells show "specific" cytological features.

Our results show that over 40% (66/157) of the DCIS cases are not of pure architectural type, but in fact they are mixed. Approximately half of the solid (51%) and micropapillary (50%) cases in our series are high grade. These values are statistically significant when compared to the occurrence of high grade cribriform DCIS, of which only 28% are high grade.

Just under half (45%) of the micropapillary and nearly two-thirds (67%) of the solid cases of DCIS are associated with comedonecrosis, while only a quarter (26%) of the cribriform cases of DCIS are associated with comedonecrosis. These differences are also statistically significant as shown above. The micropapillary type is the rarest one, occurring seldom as a pure form with less than 3% of all cases of DCIS and less than 5% of DCIS cases with a single pattern being pure micropapillary ones.

Slightly more than half (54%) of the solid and almost a third (30%) of the cribriform cases occur on their own, whereas in only 10% of the cases the micropapillary type occurs on its own.

Low grade micropapillary and solid DCIS were very rare in our series (5% and 7%, resp.).

Our results can be translated into the newly accepted DIN system by replacing the nuclear grade value with the equivalent DIN [10].

5. Conclusions

After carefully observing and analysing our data, we draw the conclusion that in many cases the pattern of growth may be a continuum, starting as micropapillary, with papillae then either joining one another to form arches resembling the cribriform pattern or even continuing to proliferate until a solid sheet of cells fills the entire lumen.

As necrosis occurs toward the tips or on the sides of the micropapillary structures, the lesion becomes intermediate grade. With progression, nuclear pleomorphism and a comedo-type necrosis appear, and the lesion then qualifies as a high grade DCIS.

We therefore believe the study of the determinants of growth pattern in DCIS would be the key to unravelling the diverse, often nonconcordant evidence one encounters in the literature.

Disclosure

The work is original and the paper has not been published in other journals. No human experimentation involved or ethical issues are envisaged.

Conflicts of Interests

No conflicts of interest or financial gains are envisaged by any of the authors.

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