

Antonio Toesca

27.1 Introduction

Ductal intraepithelial neoplasia (DIN) and lobular intraepithelial neoplasia (LIN) are the new acronyms that many authors now use to replace the traditional definition of ductal or carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS) of the breast, respectively. This is because some authors [1] found it difficult to accept the intraductal proliferation of tumor cells being defined as a malignant tumor and others [2, 3] consider that in these cases, the “N” and “M” categories should not be applied and that there is therefore no reason to keep them within the TNM classification, as “intraductal carcinoma” [4].

In this chapter we shall examine DIN1c to DIN3 (DCIS any grade) considering the rest of the intraepithelial neoplasias, such as flat epithelial atypia (DIN1a) and atypical ductal hyperplasia (DIN1b), as risk factors of variable magnitude in the subsequent development of “in situ” breast cancer. Considering that LIN does not require treatment by way of cancer therapy, careful observation is needed to watch for any signs of invasive breast cancer. In addition, strategies such as medication or surgery can be taken into consideration to reduce the risk of breast cancer in the future. Not so long ago, most patients with DIN presented with clinical symptoms, such as breast mass, bloody nipple discharge, or Paget’s disease [5].

Today, most lesions are non-palpable and generally detected by imaging alone, due to the widespread use of mammography screening programs [6].

Issues in the management in DIN include: type of surgery performed in terms of indications for breast conservative surgery (with or without radiation therapy), indications for mastectomy with reconstruction, assessment of margins, and staging of the axilla.

27.2 Breast Conservative Surgery With or Without Radiation Therapy

Until approximately 20 years ago, the treatment for most patients with DIN was mastectomy. Today, almost 70% of newly diagnosed patients with DIN are treated with breast preservation [7].

Multiple trials have demonstrated the feasibility and oncologic safety of breast conservative surgery (BCS) in DIN [8], and BCS is used in DIN for similar indications to those for invasive carcinoma [9, 10].

Breast conservative surgery is performed particularly for those patients with small solid masses, mammographically detected lesions, or limited microcalcification areas resulting in an extremely high survival rate and low absolute risk of local recurrence. At present, mastectomy is performed in about 30% of DIN patients, BCS without RT in about 30%, and BCS followed by RT in about 40% [11].

By the early 1990s, with the launch of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-17 trial, which specifically looked at excision versus excision plus radiotherapy (RT), BCS joined mastectomy as a standard option of care in breast cancer surgery management [12].

Clearly, the benefit of RT for decreasing ipsilateral breast tumor recurrence is well established; however, none of the most important prospective studies such as NSABP B-17, the European Organization for the Research and Treatment of Cancer (EORTC) 10853 trial, the Swedish Breast Cancer Group, and the UK Coordinating Committee on Cancer Research (UKCCCR) showed an overall survival benefit, and there was no decrease in metastasis [2, 3, 13–16].

In the current management of DIN patients, physicians are faced with the issue of whether to recommend radiotherapy and/or tamoxifen treatment to their patients in addition to surgery. To aid in this decision, a number of factors are taken into account, including patient age and tumor margins, grade, and size, but the evidence to support these and other potential features as prognostic is variable [17].

A. Toesca, M.D.
European Institute of Oncology,
Via Ripamonti 435, Milan 20141, Italy
e-mail: antonio.toesca@ieo.it

Considering that the goal in the management of DIN is to maximize local control with the least-aggressive treatment, avoiding overtreatments and multiple important risk factors can be involved in the choice of performing radiation therapy for some low-grade low-risk neoplasia such as age, multifocality, margin status, Ki-67, and menopausal status as prognostic factors for local events [18].

The most significant predicting factor for local recurrence is the presence of multifocality. In fact, a recent meta-analysis of three randomized control trials (RCTs) and two observational studies including 3895 patients showed an increased risk of recurrence in patients diagnosed with multifocal DIN of any grade (range from 1.55 to 2.97 in RCTs and from 1.8 to 6.0 in observational studies) [19]. Moreover, a large observational study of 260 patients treated by BCS alone or BCS plus external radiation therapy concluded that multifocality is an independent risk factor for the development of ipsilateral breast tumor recurrence (IBTR) after BCS for any DIN with or without RT [20].

Although many studies have the bias of retrospective material, and often have no comparison to a radiotherapy group, several previous reports have studied the association between age and risk of IBTR after BCS for DIN.

In a study by Lagios [21], low-grade disease, not greater than 25 mm, discovered mammographically and excised with at least 1 mm margins, revealed a 12% IBTR rate at 5 years and 16% at 10 years, with no breast cancer-related deaths and no systemic recurrences for patients treated without RT [22].

Adverse prognostic factors for DIN outcomes include younger age at diagnosis, symptomatic presentation (i.e., palpable), larger tumor size, higher nuclear grade, presence of comedo necrosis, and positive margins on excision. The benefit of radiation based on the presence of these factors has been a topic of controversy. The retrospective work of Silverstein in the development of the Van Nuys Prognostic Index was the first attempt at stratifying risk and prescribing a different surgical and RT regimen for DIN according to age, tumor size, pathological classification, and margin width [23–25].

The Van Nuys Prognostic Index combines several clinicopathological factors to aid decision-making regarding the use of radiotherapy and completion mastectomy after lumpectomy. The original VNPI was introduced in 1995, and it classified DCIS cases according to nuclear grade and the presence of comedo necrosis. Subsequent revisions of the VNPI included tumor size, margin width, and patient age in the scoring system. In its current format, scores of 1–3 each are assigned for patient age, tumor size, margin width, and tumor class (the nuclear grade and presence/absence of comedo necrosis), giving a sum of 4–12, with a score of 4 being associated with the lowest recurrence risk [26]. High mammographic density (at least 75% density) has been associated with a relative risk of 2.8 (95% CI 1.3–6.1) for the develop-

ment of local recurrence in patients treated with local surgical excision and radiotherapy [27].

A meta-analysis conducted by Wang et al. again reported multifocal DIN to be associated with an increased risk of ipsilateral recurrence compared with unifocal tumors (overall risk estimate 1.95, 95% CI 1.59–2.4063) [28].

In conclusion, the use of RT for patients treated with BCS is still a matter of debate. In a recent Saint Gallen Consensus Conference, the majority of the panel supported radiation after complete excision of ductal carcinoma in situ (DIN) but was prepared to consider its omission for some elderly patients and for those with low-grade low-risk DIN [29].

27.3 Mastectomy and Reconstruction

In the past, when mastectomy was common, reconstruction was uncommon; if it was performed, it was generally done so as a delayed procedure. Today, reconstruction for patients with DIN treated by mastectomy is common; when it is performed, it is generally done immediately, at the time of mastectomy.

The evolution of mastectomy techniques enables patients requiring mastectomy and patients undergoing risk-reducing surgery to benefit from advances in oncoplastic surgery, with improved cosmetic outcomes and reduced psychological impact.

In the past, when a mastectomy was performed, large amounts of skin were discarded. Today, it is considered perfectly safe to perform a skin-sparing mastectomy for DIN and in many instances, nipple-areola sparing mastectomy.

In the past, there was little confusion. All breast cancers were considered essentially the same, and mastectomy was the only treatment. Today, all breast cancers are different, and there is a range of acceptable treatments for every lesion. For those who choose breast conservation, there continues to be a debate as to whether radiation therapy is necessary in every case. These changes were brought about by a number of factors. Most important were increased mammographic utilization and the acceptance of breast-conservation therapy for invasive breast cancer.

The widespread use of mammography changed the way DCIS was detected. It also changed the very nature of the disease detected, by allowing us to enter the neoplastic continuum at an earlier time. Until the 1980s, the treatment for most patients with any form of breast cancer was generally mastectomy. Since that time, numerous prospective randomized trials have shown an equivalent rate of survival with breast conservation therapy for selected patients with invasive breast cancer. On this basis, it made little sense to continue treating a lesser disease (DIN) with mastectomy while treating the more aggressive invasive breast cancer with breast preservation.

Recently, numerous investigators have assessed the value of preoperative MRI in DIN, and today the debate centers on whether or not the addition of MRI to conventional mammograms and ultrasound in the preoperative evaluation of DIN would result in a better prediction of disease extent and thus potentially improve the rate of mastectomies. Doyle et al. [30] clearly stated that they saw a statistically significant improvement with concordance between the predicted and pathologically proven extent of DIN when using a mammography-MRI combination, compared with using mammography alone. They conclude that the addition of MRI to mammography in preoperative evaluation for DIN does improve concordance with the final pathology. This is a promising result in terms of the potential for MRI to aid decision-making in DIN-diagnosed patients, given that one of the key preoperative decisions is whether or not one should proceed with BCS or with mastectomy.

27.4 Assessment of Margins

The definition of positive margins has varied widely, making data synthesis challenging. In one meta-analysis of 4660 patients in 21 studies who underwent partial mastectomy and radiation for DIN, recurrence rates were as high as 10% and showed a correlative increase in rates of recurrence with reduced thresholds for margin positivity [31].

Yet, Houssami et al. found that when the data were adjusted for the administration of adjuvant therapy, there was no significant decrease in local recurrence rates for 1-, 2-, and 5-mm margins [32, 33].

The overview of the four prospective randomized trials of RT for DCIS reported that negative margins are associated with a lower risk of recurrence [15].

Solin et al. [34] reported that in a multivariable analysis of 1003 women with mammographically detected DCIS treated with BCS and RT, and median follow-up of 8.5 years, margin status and age were the only statistically significant factors associated with recurrence. Compared with negative margins, positive margins (tumor on ink) had an HR of 3.35 (P¼ 0.00035), and close margins (defined as <2, <2–3, or <3 mm) had an HR of 1.9 (P¼ 0.03). As well demonstrated by Shaikh et al. [35] in a large series of women with DIN, where numerous factors were controlled for, they found that margin width was strongly associated with risk of recurrence for women undergoing BCS who do not receive RT. In contrast, they found no association among those who do receive RT, demonstrating a differential association of margin width and recurrence, depending on adjuvant treatment. These results support the conclusion that obtaining wider negative margins may be important in reducing the risk of recurrence in women who choose not to undergo RT or some adjuvant systemic therapy and may not be necessary in those who receive RT.

27.5 Staging of the Axilla

Over the past decade, sentinel lymph node biopsy has widely replaced axillary lymph node dissection as the preferred method of nodal staging for breast cancer. In recent years new data confirm that sentinel node biopsy for DIN should be limited primarily to those patients who require mastectomy. While earlier studies suggest a number of possible indications such as high-grade tumor, large lesion, palpability, inability to rule out invasion, etc., the percentage of micro-invasion in the resected specimen and therefore consequent percentage of positivity of the sentinel lymph node are described as less than 1% [36].

With BCS, the risk of second surgery after accidental diagnosis of infiltrating carcinoma is very low. In the event of invasion after BCS, a sentinel node biopsy is always technically feasible. The situation is different when mastectomy is performed considering that a second surgery on the axilla could be technically more problematic.

In 2014, ASCO updated recommendations on the use of sentinel node biopsy for patients with DIN [37] stating that sentinel node biopsy is recommended when mastectomy is performed. Concerning the staging of the axilla for breast conserving surgery, the panel also recommended: (1) sentinel node biopsy only for minimally invasive breast cancer demonstrated on the core needle biopsy, (2) for a lesion highly suspicious of invasive cancer, or (3) in case of an area of DCIS on imaging >5 cm.

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