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Overview

Pathological Controversies in Breast Cancer: Classification of Ductal Carcinoma *In Situ*, Sentinel Lymph Nodes and Low Volume Metastatic Disease and Reporting of Neoadjuvant Chemotherapy Specimens

E. Provenzano [*†], J.P. Brown [‡], S.E. Pinder [‡]

[*] *Department of Pathology, University of Melbourne, Parkville, Victoria, Australia*
[†] *Focus Pathology, South Yarra, Victoria, Australia*
[‡] *Breast Pathology Research, Research Oncology, Division of Cancer Studies, Kings College London, London, UK*

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Abstract

The pathological classification of breast cancer is constantly being updated to reflect the advances in our clinical and biological understanding of the disease. This overview examines new insights into the classification and molecular biology of ductal carcinoma *in situ*, the pathological handling of sentinel lymph node biopsies and the identification of low volume disease (micrometastases and isolated tumour cells) and the handling and reporting of specimens after neoadjuvant therapy. The molecular subtypes of invasive breast cancer are also represented in ductal carcinoma *in situ*. It is hoped that alongside traditional histological features, such as cytological grade and the presence of necrosis, this will lead to better classification systems with improved prediction of clinical behaviour, in particular the risk of progression to invasive cancer, and enable more targeted management. Sentinel lymph node biopsy is now the standard of care for early stage breast cancer in clinically node-negative patients. However, the handling and reporting of these specimens remains controversial, largely related to the uncertainties regarding the clinical significance of micrometastases and isolated tumour cells. The increasing use of neoadjuvant therapies has introduced challenges for the pathologist in the handling and interpretation of these specimens. Grading the tumour response, particularly the identification of a complete pathological response, is prognostically important. However, there is still marked variability in reporting these specimens in routine practice, and consensus guidelines for the histopathology reporting of breast cancers after neoadjuvant chemotherapy based on robust, validated evidence are presently lacking.

Key words: Breast cancer; ductal carcinoma *in situ*; histopathology; neoadjuvant chemotherapy; sentinel lymph nodes

Statement of Search Strategies Used and Sources of Information

All searches were carried out using the PubMed Entrez database: DCIS – the terms used were 'DCIS and molecular subtypes', 'DCIS and classification' and 'breast cancer and molecular subtypes'; SLNs – the terms used were 'breast cancer and SLN', 'breast cancer and sentinel lymph node', 'breast cancer and micrometastasis' and 'breast cancer and isolated tumour cells'; neoadjuvant chemotherapy – the terms used were 'breast cancer and neoadjuvant chemotherapy and histopathology'. Additional papers cited in other articles were also obtained.

Introduction

Pathological specimen handling, diagnosis and the classification of disease are frequently updated in the light of increasing understanding of its molecular biology, as well as changes in clinical practice. Here we aim to address three areas of present uncertainty: the classification of ductal carcinoma *in situ* (DCIS); sentinel lymph node (SLN) handling and reporting; and specimen handling and classification of breast excision specimens from women who have received neoadjuvant therapies, particularly with regard to the quantification of tumour response.

Author for correspondence: E. Provenzano, Focus Pathology, Ground Floor, 60 Wilson Street, South Yarra, Victoria 3141, Australia. Tel: +61-3-9856-3201; Fax: +61-3-9804-8088.
E-mail address: elena.provenzano@focuspathology.com.au (E. Provenzano).

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Classification of Ductal Carcinoma *In Situ*

The biological and genetic heterogeneity of invasive breast cancer is mirrored by its precursors, such as DCIS, with enormous histological variety in DCIS between patients. When a precursor of invasive carcinoma is the sole lesion within a surgical sample, it is important to predict as accurately as possible its probable behaviour to direct the clinical management at this 'curable' stage. However, the identification of clinically relevant subgroups predictive of progression to invasive carcinoma remains elusive and methods for better classifying DCIS are of renewed interest.

The minimum pathological data for DCIS include the cytonuclear grade, reported as low, intermediate or high [1]. This has been shown to predict the likelihood of recurrence, for example in the UK DCIS I randomised clinical trial [2]. Architecture is recorded as solid, cribriform, micropapillary, flat or papillary, as is the presence of comedo-type necrosis and lesion size. Grading systems that combine the cytonuclear grade and the presence or absence of comedo-type necrosis also correlate with recurrence [3]. Although radiotherapy in addition to breast-conserving surgery (BCS) reduces the local recurrence of DCIS [4–6], as does adequate resection, no consensus exists as to whether all patients require radiotherapy, or what constitutes 'adequate' in terms of the distance to margins. However, these pathological and clinical features alone lack specificity for the reliable prediction of outcome and not all women in the UK with DCIS, including high-grade DCIS or that which extends to margins, receive radiotherapy after BCS [7]. Attempts have been made to achieve greater precision in predicting outcome by combining pathological features with other factors, such as lesion size and the distance to margins, but these have not been universally adopted, despite more recent updates [8].

The United Kingdom Coordinating Committee on Cancer Research (UKCCCR) DCIS working party [2] have identified a pattern of DCIS with high-grade, solid architecture (>50%) and extensive necrosis (>50%) linked to a worse outcome, and have proposed a novel pathological grading system using this combination of features. This requires further validation but seems to identify a clinically relevant group of patients with high-risk disease. In addition, the division of low- and intermediate-grade DCIS in the UK DCIS I trial showed less clinical relevance than anticipated, with similar rates of local ipsilateral recurrence as *in situ* or invasive disease, although there was a relatively small number of cases. Nevertheless, the lack of difference between low- and intermediate-grade DCIS in this trial supports the view that these lesions may potentially be suitable for a proposed trial of active surveillance versus standard surgical excision, and that they behave differently to high-grade DCIS.

Studies of allelic imbalance also show that low/intermediate- and high-grade DCIS are genomically different [9]. Most low-grade DCIS has a distinct genomic profile, often exhibiting 16q deletions [10], whereas high-grade DCIS shows a wider spectrum of genomic aberrations, including gains on 17q and 11q, and possible 13q losses [11]. Genomic disparities have also been identified between DCIS and invasive tumours, such as loss of 3q, 6q, 8p and 11q gains in 5q, 16p, 19q and 20 found in invasive tumours but not DCIS [12]. Invasive breast cancers are genetically complex, and genomic studies have shown that invasive breast cancer is a group of diseases that can be separated into intrinsic molecular subgroups. The number and distribution of these subgroups still needs to be clarified, with the original five clusters proposed by Perou *et al.* [13] more recently being extended to 10 possible groups [14]. These molecular subtypes can also be recognised in DCIS using similar genomic methods or immunohistochemistry as a surrogate [15–18]. However, few genomic systems have been applied to predict the behaviour of DCIS. The histological assessment of grade was replaced by genomic grade within the Van Nuy's Prognostic Index and found to predict early relapse in a small series [19]. These authors also combined a proliferation marker (Ki67) with the clinical features of the Van Nuy's Prognostic Index, but found no additional value.

It should be remembered that there are pathways to invasive carcinoma other than through DCIS; flat epithelial atypia, lobular carcinoma *in situ* and microglandular adenosis [20] are regarded as definitive but non-obligate precursors. Thus, there are differences in the distribution of intrinsic subtypes between DCIS and invasive carcinoma, and in the overall frequency of specific molecular abnormalities (e.g. *Her2* gene amplification).

In order to determine predictive factors in the transition from premalignant to invasive, attention has also turned to the role of the microenvironment surrounding DCIS [21]. Genomic changes in cancer-associated stromal cells and myoepithelial cells are indicative of the complexity in this translational phase [22]. For example, a decreased expression of CD10 in DCIS-associated myoepithelial cells has been implicated in a lower disease-free survival (DFS) [23]. It is thus evident that DCIS has epigenetic, genomic, morphological and microenvironmental features that all contribute to the heterogeneity of such lesions and that a combinatorial approach to defining factors of disease progression is required. Research is ongoing to define combinations and patterns of biomarkers that will assist clinicians and patients in choosing the optimum approach for each woman.

Sentinel Lymph Node Assessment and the Classification of Isolated Tumour Cells and Micrometastases

The introduction of SLN biopsy (SLNB) has revolutionised the management of the axilla in patients with early stage breast cancer, and is now the accepted method of axillary staging in clinically node-negative disease [24]. The SLN represents the first node(s) draining a cancer and, therefore, to harbour metastasis [25]. The receipt of fewer nodes, and the increased importance of accurate assessment to minimise false-negative results, has resulted in more intensive pathological sampling of SLNs with 'stage migration' due to increased detection of low volume disease, the clinical significance of which remains controversial [26–31]. SLNB