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Improving DCIS diagnosis and predictive outcome by applying artificial intelligence

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Abstract

Breast ductal carcinoma in situ (DCIS) is a preinvasive lesion that is considered to be a precursor to invasive breast cancer. Nevertheless, not all DCIS will progress to invasion. Current histopathological classification systems are unable to predict which cases will or will not progress, and therefore many women with DCIS may be overtreated. Artificial intelligence (AI) image-based analysis methods have potential to identify and analyze novel features that may facilitate tumor identification, prediction of disease outcome and response to treatment. Indeed, these methods prove promising for accurately identifying DCIS lesions, and show potential clinical utility in the therapeutic stratification of DCIS patients. Here, we review how AI techniques in histopathology may aid diagnosis and clinical decisions in regards to DCIS, and how such techniques could be incorporated into clinical practice.

Keywords

DCIS; Breast cancer; Pathology; Image analysis

1. Introduction

Ductal carcinoma in situ (DCIS) is a preinvasive breast lesion, where tumor cells are restricted within the duct by a myoepithelial-basement membrane barrier (Fig. 1A). DCIS is considered a precursor to invasive breast cancer (IBC), though not all DCIS lesions will progress to invasion within a patient's lifetime. Only 20–50% of women with untreated DCIS will ultimately develop IBC [1]. Nevertheless, clinical management involves

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aggressively treating all patients presumptively as though they will progress. Consequently, many women with DCIS are likely overtreated [2]. Histological classification systems aim to classify DCIS according to a combination of features, such as the degree of nuclear atypia and the presence of necrosis [3], into cases that are more or less likely to progress to, or recur as, invasive disease [4,5]. However, even low-risk DCIS has an equal potential to progress, though the time to progression may be greater [6]. Histological grading alone may be insufficient to predict an individual patient's risk to progression. Therefore, there is an unmet clinical need for objective prognostic classification systems that encapsulate unique histological features and molecular phenotypes to improve risk stratification of DCIS.

Artificial intelligence (AI) has emerged as a tractable approach to transform histological image interpretation and analysis through its ability to learn and recognize unique patterns and relationships within tissues. The most common AI methods used for image analysis include the segmentation of cells and nuclei within tumor and stromal regions, and the classification of cell phenotypes and tissue features (Fig. 1B–D). This information is then used to facilitate the accurate identification of DCIS amongst other preinvasive breast lesions, as well as to establish the prognostic outcome and predictive behavior of DCIS (Fig. 1E). Importantly, such methods show promise in improving these traditional classification systems by incorporating heterogeneity within DCIS tissues [7], and by overcoming the intraoberserver and interobserver variability of pathologists in assigning scores to features of the histological grading systems [8]. In this mini-review, we highlight how AI imaged-based approaches in histopathology may aid the identification of DCIS lesions, and discuss their potential to improve the therapeutic stratification of DCIS patients. We review how such approaches could be incorporated into clinical practice and outline outstanding challenges in the field.

2. Image analysis in DCIS diagnosis

Proliferative lesions of the breast, which include hyperplasia, atypia and DCIS, are associated with varying risk of breast cancer [9] and therefore, accurate pathological classification has major implications for patient management. Most patients with hyperplasia or atypia have a minimal increased risk of cancer and receive no treatment and clinical management involves continuation of routine breast screening, while patients with DCIS who are more likely to progress or recur with invasive disease, undergo aggressive therapy including surgery with radiotherapy and/or hormone therapy, similar to women diagnosed with IBC [10]. Failure to provide accurate diagnostic oversight can lead to either untreated cancer or unnecessary administration of aggressive therapies. Though accurate diagnosis is essential, diagnostic disagreements are remarkably high for these preinvasive lesions. Indeed, there is often a disagreement by pathologists with their initial diagnosis when reassessing the same specimen, and concordance between pathologists for these preinvasive lesions is lower than for IBC diagnosis [11]. AI in breast diagnostics can improve radiologists' performance in detecting breast cancers [12], and the development of such methods for the accurate and reproducible identification of DCIS in histology images has high potential to augment pathological assessment at diagnosis.

The pathological distinction between these breast lesions currently depends on multiple architectural and cytologic features, with nuclear atypia being particularly important in distinguishing normal or benign hyperplasia from malignant lesions. For instance, IBCs display disruption to the tissue architecture with tumor clusters infiltrating the breast stroma, that often show a high degree of nuclear density and variability. While AI in histopathological analysis of DCIS is an emerging field, there is already encouraging success by several groups that demonstrate the ability to differentiate benign lesions from DCIS using nuclear segmentation and feature extraction (AUC of 0.858 and 0.918) [13,14]. Another approach utilized tissue features to correctly identify whether DCIS or atypia was present more frequently than pathologists. Such that, the sensitivity of the machine-based approach was between 0.88 and 0.89, while the pathologists' average sensitivity was 0.70, where a higher sensitivity score indicates a greater likelihood that a diagnosis and classification is correct [15]. Similarly, nuclear morphological changes in myoepithelial cells have also been successful in differentiating DCIS from normal breast and benign lesions with a high accuracy of 90.9% [16]. The presence of the myoepithelial cell layer is an important distinction of DCIS from IBC. This is often difficult to identify on H&E images due to attenuation of myoepithelial cells in DCIS, and immunohistochemical (IHC) staining for cytokeratin's is often utilized to facilitate this distinction. Thereby, such computational pathology algorithms may replace the need for IHC staining in these instances. The importance of AI-based diagnosis techniques has led to the generation of large cancer databases that contain histopathology images such as the NIH Cancer Genome Atlas (TCGA) [17], Tissue Microarray Database [18] and BreakHis [19], amongst others. Such databases provide a large number of high-quality histology images and associated clinical data in order to facilitate the development of novel techniques. This is also key to ensuring existing models have been applied to validation datasets in order to determine their clinical utility.

The diagnostic classification of benign breast lesions, breast cancer precursors and breast cancers largely depend upon the histological appearance of epithelial cells. However, the breast stroma appearance also contributes to the pathologists' diagnostic impression, including the recognition of invasion, yet these subjective assessments have not been formally classified. Given that the stroma surrounding DCIS is different to normal breast [20], it is likely that morphological analysis of the stroma could aid diagnosis. Development of robust algorithms for discriminating patterns of normal and tumor-associated stroma in histology images is complex, partly as stromal alterations are often difficult to characterize and quantify by H&E alone. Indeed, studies aimed at distinguishing breast lesions by stromal characteristics utilize multi-photon microscopy with second-harmonic generation (SHG) [21], although promising, these approaches may not be as readily available in the clinical setting. Validated morphological criteria for classifying stroma are currently undefined for clinical diagnosis. However, a recent approach successfully classified breast biopsies as benign or malignant based solely on analysis of the stroma in H&E images (AUC of 0.962) [22]. Such methods may also assist in the identification of stromal tissue that should be included in tumor margins, given the role of the stroma in promoting aggressive tumor behavior [23–25]. Moreover, these methods may extend to identifying women at high risk for breast cancer development. Women with high mammographic density (MD) have

an increased lifetime risk of developing breast cancer [26]. Indeed, high MD tissues are characterized by greater amounts of collagen that is more oriented, fibrillar and stiff [27]. It seems intuitive that such AI techniques that may differentiate between breast precursor lesions that are at higher risk of developing invasive cancer, could also stratify women at high risk for malignant transformation based on stromal characteristics.

3. Image analysis in DCIS prognosis

DCIS is considered a precursor to IBC, though it is established that only certain groups of DCIS will progress or recur [1]. Therefore, it is likely that a group of women with DCIS may forego more aggressive treatments such as surgery and radiotherapy, which have been shown to decrease the incidence of recurrence and development of invasive cancer [28]. Indeed, several clinical trials, such as COMET (USA), LORIS (UK), LORD (Europe), and LARRIKIN (Australia and New Zealand), are currently underway to examine the effectiveness of active monitoring (with optional hormonal therapy) in women with low-risk DCIS [29]. However, current clinicopathological features used to stratify DCIS patients, such as patient age, nuclear grade, growth pattern, tumor size and associated necrosis are unable to accurately predict progression and recurrence risk [30,31]. In addition, some of these pathological features are subjective and there is low concordance between observers. For instance, a recent survey of breast pathologists documented marked variability in definition of comedo-necrosis [32]. Thus, identification of novel histological features and molecular phenotypes that may be assessed in an objective and quantitative manner to improve therapeutic stratification of DCIS, and refine the entry criteria for existing surveillance DCIS trials is essential.

Studies to date have shown promise for novel stratification of DCIS patients by incorporating nuclear heterogeneity [7], spatial mapping of cell types [33] and identification of stromal features [34]. Such studies have shown that the objective determination of nuclear grade may be a predictive factor for DCIS recurrence [35,36]. DCIS lesions display considerable heterogeneity in nuclear grade within a single tissue sample [37], which is likely to complicate pathological analysis as it is not formally acknowledged in current classification systems, though it is likely to influence tumor progression and recurrence risk [5]. Our recent study utilized a semi-automated image analysis method to quantify heterogeneity in DCIS nuclear morphology within a tissue [7]. This AI approach identified subgroups within the current classification system of DCIS, indicating that these traditional groups for nuclear grade (1–3) may be an oversimplification. Further studies are on-going to establish whether these subgroups have predictive value and how algorithms to quantify nuclear heterogeneity may be incorporated into pathological reporting criteria.

Qualitative assessment of histological grade, single marker studies and bulk tissue gene expression panels, such as Oncotype Dx [38] and The DCIS score [39], are currently used to predict DCIS recurrence or invasive progression. Nevertheless, these approaches provide limited information on different cell populations, cellular interactions and spatial context. In-depth characterization of molecular and cellular heterogeneity is important to understand the biology driving DCIS risk, as well as to identify novel prognostic biomarkers. Indeed, studies investigating the immune infiltrate in DCIS using multiplex staining have identified

different profiles that interact with distinct patterns of epithelial cells [33] and associate with a high-risk for recurrence [40]. Moreover, tumor infiltrating lymphocytes (TIL) in DCIS have been associated with aggressive clinical features, and TIL density and localization are predictive features of recurrence and progression [41]. Importantly, the spatial localization and density of TILs in DCIS may be characterized by automated detection on a simple H&E image [42,43] and guidelines for standardized reporting currently exist [44], suggesting their inclusion into pathological evaluation for patient stratification is feasible.

Quantitative studies assessing DCIS risk would benefit by also incorporating the complexity of the tissue architecture. One such study developed a risk classifier based on the spatial relationships between normal breast ducts, DCIS lesions, lymphocyte regions, blood vessels and stroma, that was able to predict 10-year risk recurrence (accuracy of 0.85 in validation set) [45]. Given the importance of the stroma in breast cancer progression, many studies have focused on developing a stromal signature for prognostic outcome. Indeed, a collagen fiber alignment signature, known as tumor-associated collagen signatures (TACS), has been used to predict cancer prognosis [24]. The TACS phenotypes describe the increased deposition of collagen surrounding a tumor (TACS-1), the progressive alignment of collagen fibers tangentially around the tumor (TACS-2) and the radial alignment of fibers that facilitate tumor cell invasion (TACS-3) [46]. In support of this in DCIS progression, we have shown that collagen is progressively more linearized and stiffened in DCIS compared to normal, which increases with invasive development [20]. The quantitative assessment of collagen perpendicular and more densely packed to DCIS lesions is predictive of invasive recurrence [47,48]. Many other studies characterizing DCIS tissues exist and are essential for elucidating the behavior of DCIS however, we have focused our review only on those that incorporate AI methods. These AI approaches are in the early stages, and further work is required to develop algorithms whose prognostic value is determined on cohorts of DCIS with long-term clinical follow-up.

4. Implementation and challenges in clinic

AI has the potential to improve risk stratification of DCIS patients. Similarly, quantitative image analysis techniques will continue to provide a more detailed description of features and heterogeneity in other tumor types to improve cancer patient management overall. AI approaches also have the potential to enhance standard pathological practice [49]. With advancing imaging technology, highly detailed tissue images with high pixel resolution are easily obtained. The generation of whole-slide images (WSI) will enable the development of tissue archives which will facilitate continued medical education and pathologist training, clinicopathological review conferences and tumor boards for consultation of cases. Most importantly, AI has the potential to help simplify routine tasks to reduce the time spent examining samples. For example, such image analysis approaches may estimate the quantity of tumor cells in a tissue. Traditionally, pathologists inspect stained tissue slides to determine tumor cellularity, this approach is not only laborious but also highly subjective due to intraobserver and interobserver variability. Thus, AI approaches will also address the concordance within and between pathologists.

Despite their promise to improve DCIS patient management, as well as general pathological practice, AI approaches will take time to be implemented in the clinic. Several issues currently hamper the utility of the proposed histological approaches in clinical practice including; the lack of standardized feature extraction algorithms and the limited sharing of annotated images. Both standardized algorithms and annotated image datasets are essential for assuring AI methods are accurate and reproducible, and reflect the diversity of the clinical population. Indeed, while machine learning methods are highly effective with a large number of samples, they often suffer from overfitting pitfalls with limited training datasets. Moreover, many of these methods depend on supervised machine learning algorithms, trained on a set of features extracted from manually annotated H&E images. While manually annotated datasets by pathologists represent the gold standard for training, they are labor-intensive to develop. The success of these approaches therefore depends on clinical research collaboration, with the aim of accumulating large, high-quality, well annotated datasets for increasing training set size and cross-validation. Additionally, by virtue of the deep learning process, it is unclear what components may be driving many of these classifiers. This is unlike analysis by trained pathologists, who use well-documented histological features and decades of training to assess tissue images. In the case of predicting DCIS behavior, it will be important to clarify the biology directing these machine learning classifiers. Increasing model interpretability by understanding the cellular and molecular insights these classifiers learn from the data, will also make the clinical use of AI approaches more agreeable to clinicians. At present, the majority of these studies are preliminary with a retrospective design and a relatively small sample size. Moreover, many studies utilize tumor biopsies or tissue microarray (TMA) cores, which provide limited characterization as these samples do not adequately represent the heterogeneity of the patient's entire tumor. For instance, 25% of patients with DCIS on core biopsy are found to have invasive cancer upon surgical excision [50]. Thus, widespread use of WSI in pathology could provide further insights into tissue heterogeneity, which may be able to predict upstaging of DCIS to IBC prior to excision in order to better stratify patients.

A feasible first step towards digital pathology in the clinic is the utilization of WSI systems, which have been approved by the Food and Drug Administration (FDA) for diagnostic medicine. With the implementation of WSI systems comes an increasing need for reliable and user-friendly AI methods to complement the manual examination of tissues [51]. Indeed, many powerful open-source and commercial image analysis platforms are currently available to speed up the development of standardized algorithms. Some of the most common commercially available software for breast pathology includes; Roche VENTANA image analysis algorithm for IHC assays to quantify breast biomarkers [52], AstraZeneca (Definiens) Tissue Phenomics software for immunooncology profiling [53] and Visiopharm image analysis to identify cell populations and tumor regions in H&E and IHC images [54]. As these platforms operate on input from WSI scanners, it is possible these solutions may be amongst the first to be tested in the clinical setting. However, in order to obtain significant statistical evidence that a given AI image analysis method can improve clinical decision making, multi-cancer center clinical trials will be essential to assess diverse patient populations, and guidelines to support AI trials have recently been developed [55,56]. These

AI trials will be fundamental for determining the reproducibility and accuracy of such applications in order to standardize AI technology into routine clinical practice.

5. Conclusions and future perspectives

There is much evidence to support AI in providing invaluable data that will facilitate the understanding of tumor biology and support clinical decision making in the era of personalized medicine. Studies to date have shown promise for AI in identifying novel features that outperform traditional clinicopathological variables in predicting DCIS outcome. For instance, analysis of a simple H&E may allow for the stratification of patients into low- and high-risk groups that relate to their risk of IBC progression or recurrence. Although these methods are promising, they require further testing in diverse, large-scale patient cohorts with follow-up data before their clinical utility in treatment decisions can be established. The AI field should also continue to build collaborative studies in order to standardize the methods used. Moreover, with further developments in AI techniques, the integration of complex data across multiple inputs from the clinic, particularly including omics datasets, will also allow for the determination of a more comprehensive prognosis in DCIS patients. Indeed, these AI methods have also been shown to improve diagnostic accuracy, and must continue to demonstrate improvements to clinical workflow and decision making in order to move into clinical practice. Such methods have great potential to serve as a supplemental tool to pathologists. In the future, we hope that AI image analysis methods will be capable of diagnosing early changes, such as by identifying small numbers of defective cells in healthy tissue biopsies, as well as from minimally invasive techniques such as liquid biopsies, from women to identify those at high risk of cancer as a preventative strategy.

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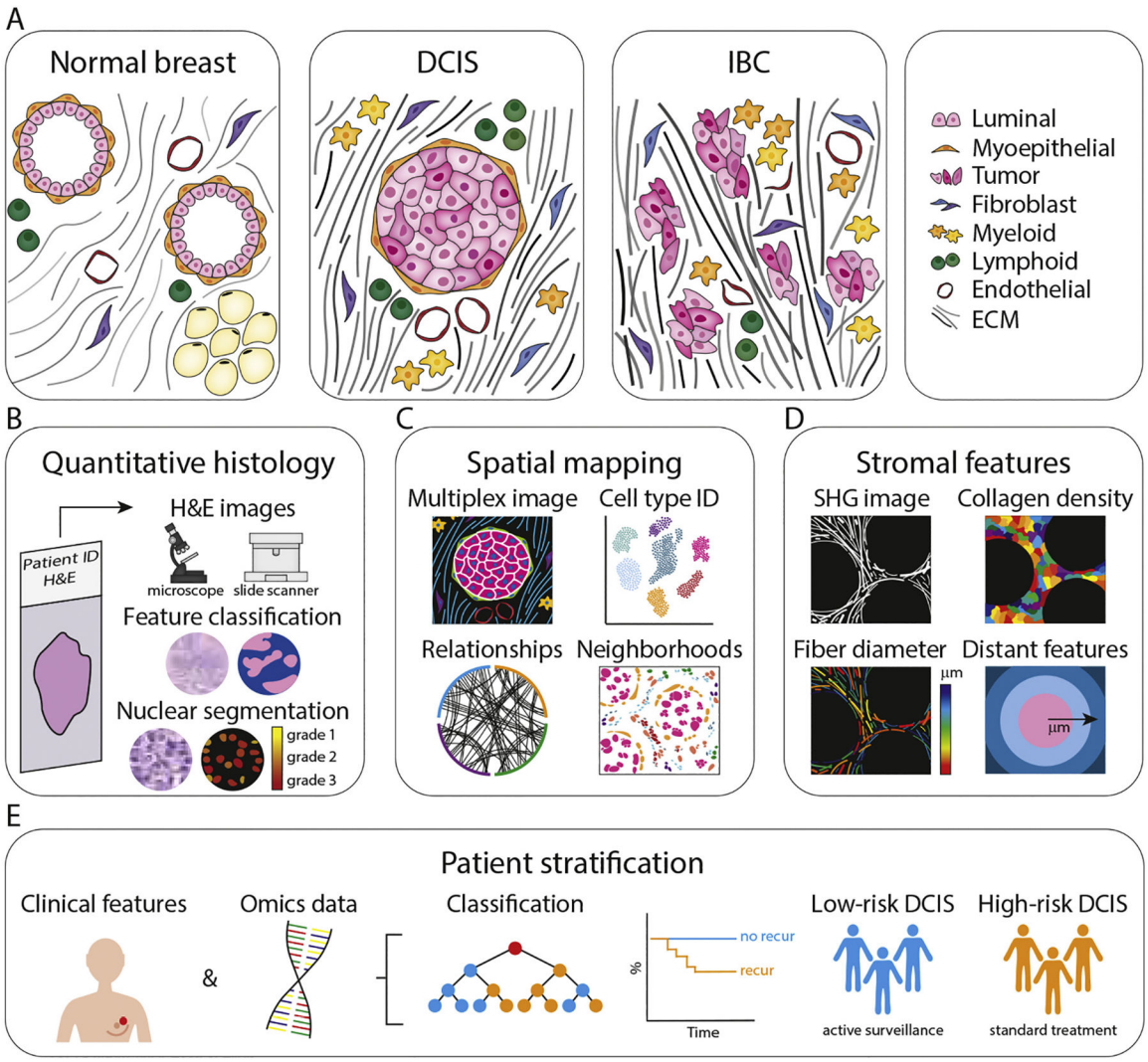

Fig. 1.

AI approaches to improve prediction of DCIS progression. a, A schematic depicting normal breast, ductal carcinoma in situ (DCIS) and invasive breast cancer (IBC). b, Overview of quantitative histological approaches that utilize hematoxylin and eosin (H&E)-stained slides. These may be used to classify tissue features or segment cells and nuclei within tumor and stromal regions. c, Cartoon depiction of features that may be extracted from multiplex analysis of tissues, including; cell phenotypes, cell-relationships and cell-neighborhoods. d, Schematic to show the types of collagen features extracted from second harmonic generation (SHG) images, such as collagen density and collagen fiber diameter, and how these stromal features may change with distance from DCIS lesions. e, Workflow to reflect that clinical features and omics data (genomics, transcriptomics, epigenomics) may be incorporated with these AI image-based findings to develop a classifier that could stratify women with DCIS into low- and high-risk groups that would determine their clinical management.