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EDITORIAL

Clinical Studies

Ductal carcinoma in situ with and without microinvasion: is there a clinically meaningful difference in outcome?

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In this issue of the Journal, Shaaban et al. report on the presentation, management, and outcome of the second largest series in the literature of cases of ductal carcinoma in situ (DCIS) with microinvasion. The cohort consisted of cases of DCIS with and without microinvasion derived from the Sloane Project, a prospective cohort of screen-detected, non-invasive breast neoplasia [1]. The cases in this study were diagnosed at multiple institutions between 2003 and 2012 and were not subjected to central pathology review. The rate of axillary lymph node metastasis was similar among patients with DCIS with and without microinvasion. However, with a median follow-up of 110 months, the frequency of both distant metastasis and mortality for patients with microinvasion was significantly higher than for patients without microinvasion (1.2% vs. 0.3%; $p = 0.01$ and 2.1% vs. 0.8%; $p = 0.005$, respectively, for distant metastasis and mortality). The authors concluded that DCIS with microinvasion is a "more aggressive disease" than DCIS without microinvasion. However, can we be certain from these results that there is a clinically meaningful difference in outcome between patients with DCIS with and without microinvasion?

The major strengths of this study are the number of cases and the length of follow-up. In total, there were 11,285 cases of DCIS, 521 of whom were diagnosed as having microinvasive carcinoma and, as noted above the median follow-up was almost 10 years. However, there are a number of limitations to this study that are similar to the limitations of almost all studies of microinvasive breast carcinoma that need to be taken into consideration before drawing firm conclusions about the impact of microinvasion on outcome.

The diagnosis and clinical significance of microinvasion has been a persistent problem for decades for several reasons. First, from a historical perspective, the definition of microinvasion has varied widely over the years [2]. Microinvasion has been variously defined simply as "evidence of stromal invasion" [3], "limited microscopic invasion invading <10% of the surface of the histologic sections examined" [4], "maximal extent of invasion ≤2 mm or invasive carcinoma comprising less than 10% of the tumour" [5], and "≤3 foci of invasion, each ≤1 mm" [6], to cite a few examples. Some of these definitions include lesions that would currently be considered frankly invasive carcinomas. It was not until 1997 that the AJCC staging system standardised the definition of microinvasion as "extension of cancers cells beyond the basement membrane…with no focus more than 0.1 cm in greatest dimension" and indicated that if there are multiple foci these should not be added together [7]. As a result of these varying definitions, the frequency of the diagnosis of microinvasion has varied widely between series. The definition of microinvasion used in the study of Shaaban et al. [1] was the 1995 definition of the UK National Coordinating Committee for Breast Pathology, i.e., a focus of invasion 1 mm or less identified within non-specialised stroma. This stromal feature was dropped from the definition in 2016, but since the cases in the current study were accrued between 2003 and 2012, presumably all participating institutions used the 1995 definition of the UK group. Nonetheless, the reported frequency of microinvasion among these institutions still varied broadly, from 0 to 25%, and decreased by more than 50% over time from 7% in 2003–2004 to 3% in 2011–2012. This suggests difficulty and/or inconsistency in application of the diagnostic criteria for microinvasion even with the availability of an established, standardised definition.

A second problem with the diagnosis of microinvasion is its recognition by pathologists. It is well established, as demonstrated in the study of Shaaban et al., that certain features of DCIS are associated with microinvasion including high nuclear grade, comedo necrosis, and greater extent of the DCIS lesion [1]. However, the histologic identification of microinvasion is notoriously difficult and is prone to both overdiagnosis and underdiagnosis. Overdiagnosis occurs because many patterns in DCIS can be mistaken for microinvasion including duct branching, involvement ("cancerization") of lobules, involvement of benign sclerosing lesions, distortion of involved spaces, tangential sectioning, crush artefact, cautery effect, extravasated mucin in cases of DCIS with mucin production, and artifactual displacement of DCIS cells due to prior core needle biopsy or specimen manipulation. Underdiagnosis can result from failure to recognise foci of microinvasion (particularly when very limited or subtle), prominent stromal chronic inflammation obscuring foci of microinvasion, and sampling error [2]. Unfortunately, no information is provided about the frequency with which additional levels were obtained to clarify the diagnosis, the frequency with which immunostains for markers used to evaluate the presence of microinvasion were employed (i.e., myoepithelial markers, cytokeratins), or the extent of sampling of the specimens in this study. Given these problems and the lack of central pathology review of the cases in the study of Shaaban et al. [1] there is likely to have been error in both directions, i.e., some patients classified as having microinvasion in fact have pure DCIS and some patients categorised as having DCIS have microinvasion. In addition, some patients in both groups may have had frankly invasive carcinomas that were undetected due to limited sampling.

As a result of varying definitions, the difficulty in histologic diagnosis, and sampling issues, the clinical significance of microinvasion remains poorly defined. The reported frequency

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of axillary lymph node involvement has varied widely among studies, ranging from 0 to 28% [8, 9]. In a meta-analysis of almost 1000 patients with microinvasion, the sentinel lymph node positivity rate was 3.2%, 4%, and 2.9%, for macrometastases, micrometastases, and isolated tumour cells, respectively [10]. This frequency of axillary nodal involvement overlaps considerably with that reported for patients with DCIS without microinvasion. Further, while some outcome studies, such as the study of Shaaban et al. [1] have shown differences in one or more outcome parameters between patients with DCIS with microinvasion and those with pure DCIS, others have not [11–15]. It should be noted that despite the large size of the study of Shaaban et al. [1] only 6 patients with microinvasion developed distant metastases. More concerning, however, is that 40 patients with a diagnosis of DCIS developed metastatic disease, suggesting underdiagnosis or under-recognition of microinvasive or even frankly invasive carcinoma in some cases classified as DCIS.

In view of the issues raised above, is it reasonable to conclude from the study of Shaaban et al. [1] that a 0.9% difference in the rate of distant metastasis and a 1.3% difference in the mortality between patients with DCIS with and without microinvasion is clinically important, despite being statistically significant? In other clinical outcome studies of breast cancer, statistically significant differences did not necessarily indicate that the difference was of clinical importance. For example, in the ACOSOG Z0011 trial of sentinel lymph node biopsy vs. axillary dissection for patients with invasive cancer and sentinel lymph node metastases, there was a statistically significant difference in 10-year overall survival of 2.7% between the two groups (86.3% for sentinel lymph node biopsy vs. 83.6% for axillary dissection, $p = 0.02$) [16]. However, this small difference has not been considered clinically meaningful, and this difference is even larger than the outcome differences between patients with DCIS with and without microinvasion in the study of Shaaban et al.

In our view, the study of Shaaban et al. [1] should be viewed as opening the door for additional, more detailed studies of the clinical impact of microinvasion in the setting of DCIS. We now accept that invasive breast carcinomas of no special type, once viewed as a single subtype, represent a highly heterogeneous group of tumours with regard to histologic features, oestrogen receptor (ER), progesterone receptor (PR), and HER2 status, proliferation rate, tumour infiltrating lymphocytes, gene expression signatures, genomic alterations, response to adjuvant and neoadjuvant systemic therapy, and risk of local and distant recurrence. In addition, the heterogeneity of DCIS without microinvasion is also well recognised. There is no reason to think that DCIS with microinvasion is not equally heterogeneous and represents a biologic spectrum, with some behaving more like pure DCIS and some behaving more like frankly invasive carcinomas. In particular, whether certain features of microinvasive carcinomas such as the number of foci of microinvasion or biomarker status (particularly HER2 overexpression) are related to outcome remains an unresolved issue and merits further study [17, 18].

Identification of a subset of patients with microinvasion at increased risk for lymph node involvement and distant metastasis remains an important clinical goal. Given the relative infrequency of microinvasion, multi-institutional studies with careful radiologic-pathologic correlation, central pathology review, assessment of biomarkers (such as ER, PR, HER2, and Ki67) and long-term follow-up are required to further define the biology of microinvasive carcinoma of the breast.

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AUTHOR CONTRIBUTIONS

Both authors were involved in the conception, writing, and review of this manuscript.

COMPETING INTERESTS

The authors declare no competing interests.