Article published online: 2021-05-23

Palpable Ductal Carcinoma *In situ*: A Paradox of Benign Mind with Malignant Action!

Ductal carcinoma *in situ* (DCIS) accounts for 30% of the cancers detected through breast screening, while it is <5% in the symptomatic population, and microinvasion (DCIS-M) is found in 10%–14% of the palpable tumors with DCIS.[1] The most common presentation is a palpable mass often with nipple discharge.[2,3] Current guidelines for the management of DCIS refer to screen detected DCIS. In this era of de-escalation of treatment for DCIS, we need to evaluate pDCIS as a distinct entity which is different from low-risk screen-detected lesions. There are no defined treatment guidelines for pDCIS or DCIS-M.

Evaluation for all women who present with a breast lump includes the triple test wherein a clinical evaluation, imaging with mammography with or without ultrasound and histopathological confirmation, is done. The role of MRI in evaluating DCIS is limited with low sensitivity ranging from 72% to 84%.[4] The management and extent of surgery are same as for early invasive cancers. The disease must be mapped accurately on imaging. However, with noncalcific DCIS, there is a higher risk of margin positivity which must be kept in mind. No prospective randomized trial has compared mastectomy to breast-conserving surgery in women with DCIS. A meta-analysis of studies published up to 1998 reported local recurrence rates of 22.5% (95% confidence interval [CI] =16.9%–28.2%), 8.9% (95% CI = 6.8%–11%), and 1.4% (95% CI = 0.7%–2.1%) for lumpectomy alone, lumpectomy with radiation, and mastectomy, respectively.[5] The lack of a difference in survival between the two approaches has led to a decline in the use of mastectomy, which is now offered to patients with multicentric disease, large lesions, other contraindications to breast conservation, or a personal preference for mastectomy, as is with invasive cancers.

pDCIS has a 10%–14% risk of harboring an invasive component. It is essential to differentiate microinvasive DCIS from multiple foci of invasive ductal carcinoma (IDC) in a background of DCIS with extensive intraductal component (EIC). There are, however, multiple definitions of DCIS with microinvasion. As per the American Joint Committee on Cancer (AJCC), the size of only the largest focus should be used to classify the microinvasion when there is more than one focus. Although multiple foci suggest higher tumor volume, the AJCC advises not to use the sum of the size of all the individual foci, and that multiple foci of microinvasion should be noted.[6] In addition to the AJCC classification, de Mascarel *et al*.[7] defined two distinct types of DCIS-M and evaluated their clinical significance. Type 1 has a single site of infiltration beyond the basement membrane, behaves similar to DCIS, and should be treated as such. Type 2, harboring numerous clusters of microinvasion, has a worse prognosis and needs to be treated more aggressively. Thus, identifying the microinvasion and number of foci is essential to planning further management in the cases of pDCIS. Various studies have evaluated factors that predict the presence of microinvasion wherein large tumor, comedo-type architecture, and estrogen receptor negativity were found to be independent predictors of microinvasion (all $P < 0.001$).[8]

The pathologist's role is critical in defining whether this is a case of pDCIS or DCIS-M Type 1 or Type 2. Thus, sampling the entire specimen and mapping entire tumor is critical to ensure that pDCIS has no invasion. For tumor mapping, the grossly visible lesion is "bread-loafed" and sliced serially at distance of 1 cm. Each slice is then cut into square sections which are labeled consecutively. This allows us to construct the entire DCIS microscopically and define size of DCIS as well as invasive tumor if any, for example, if two consecutive sections show invasive carcinoma and each sectioned is 3 mm, then 3 mm × 2 mm = 6 mm size. Furthermore, if available, radiographically guided grossing is recommended in cases of DCIS.[9]

For screen-detected DCIS, National comprehensive cancer network recommends the role of sentinel lymph node biopsy, only in cases undergoing a modified radical mastectomy. The incidence of axillary lymph node metastases with DCIS is only 1.4%, while with DCIS-M, it is higher at 5.1%.[10] Possible indications for axillary lymph node dissection are the suspicion of microinvasion, such as the presence of a clinically palpable node or palpable comedo-type DCIS. However due to the underestimation of invasion in biopsies of pDCIS, we advocate lymphatic mapping using sentinel lymph node biopsy or axillary sampling at the time of surgery, with both modified radical mastectomy and breast-conserving procedure.

Studies evaluating types of DCIS-M have suggested that patients with DCIS and DCIS-M Type 1 had better metastasis-free and overall survival than patients with DCIS-M Type 2, and patients with DCIS-M Type 2 had better metastasis-free and overall survival than patients with IDC–DCIS.[7] However, the role of adjuvant therapy in pDCIS and DCIS-M is still not clear.

Management of triple-negative and Her 2-positive disease pDCIS or DCIS-M is more controversial than that of hormone receptor (HR) positive. Tamoxifen is the standard

adjuvant therapy for HR-positive cases, recommended for 5 years.[11] The risk of subsequent invasive ipsilateral breast cancer was found to be reduced by tamoxifen versus placebo in DCIS.[11] In terms of efficacy and safety, tamoxifen and aromatase inhibitor were found comparable (91% vs. 93%). However, with varying spectrum of side effects, anastrozole was associated with musculoskeletal pain, hypercholesterolemia, and strokes, while tamoxifen was associated with muscle spasm, deep-vein thrombosis, and gynecological cancers.[12]

Notably, this entity is uncommon is Western world, and hence, no clear treatment guidelines about adjuvant chemotherapy exist. However, there is a case for adjuvant chemotherapy in pDCIS or DCIS-M. We conducted a retrospective audit of cases treated from 2005 to 2016, treated at our institution, wherein we identified 784 cases of with DCIS, DCIS-M, and early invasive cancer with EIC at our center. Among these, 740/784 (94.4%) presented with palpable breast lumps, of which 14.4% had Tis and 43.5% of DCIS had microinvasion. On follow–up, distant recurrences were noted in 5 (4.4%) patients with Tis, 3 (3.4%) with T1 mic, 21 (9.5%) with T1, and 63 (17.3%) with T2, (P = 0.00). Limited use of adjuvant chemotherapy in Tis and T1 mic may have contributed to the high distant recurrences in that group (unpublished data).

We recommend the use of adjuvant chemotherapy, especially in high-risk cases with palpable Type 2 DCIS-M (multiple foci of invasion in a background of DCIS), especially in cases with Her2/neu-positive microinvasive foci. This entity, however, being rare and with lack of high-quality guidelines merits individualized case-based discussions in multidisciplinary tumor boards.

We conclude that DCIS presenting in palpable lesions poses a clinical dilemma for the use of adjuvant therapy, especially in cases with DCIS-M. We thus need to reconsider grossing techniques and the role of adjuvant chemotherapy in treating pDCIS. It seems prudent to categorize DCIS-M as a small invasive tumor with a generally favorable outcome. However, at times, it can behave like "the one with benign mind but malignant action" and merits individualized precision care.

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Submitted: 05-Mar-2020
Accepted in Revised Form: 28-Apr-2020
Published: 13-Jun-2020

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Website: www.ijmpo.org

DOI: 10.4103/ijmpo.ijmpo_88_20

How to cite this article: Nair NS, Shet T, Kirti K, Bajpai J. Palpable ductal carcinoma *in situ*: A paradox of benign mind with malignant action! Indian J Med Paediatr Oncol 2020;41:244-6.