

## Practical consensus recommendations for Paget's disease in breast cancer

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## Abstract

Paget's disease of the breast is a rare type of cancer of the nipple-areola complex and that is often associated with an underlying *in situ* or invasive carcinoma. Diagnosis and treatment of Paget's disease is controversial. Expert oncologists discuss on the update on the approaches of Paget's disease diagnosis and its treatment options. This expert group used data from published literature, practical experience and opinion of a large group of academic oncologists to arrive at this practical consensus recommendations for the benefit of community oncologists.

**Key words:** Biomarkers, magnetic resonance mammography, radiation therapy, SLNB, wedge biopsy, wide local excision

## Introduction

Paget's disease is a rare form of breast neoplasm that is associated with approximately 3% of all breast cancers.<sup>[1]</sup> It is much more frequently found in females than males, though it can be found in men, with some series suggesting worse prognosis in men.<sup>[2]</sup> In 1856 Velpeau described the eczematous lesions of Paget's disease,<sup>[3]</sup> but Sir James Paget first described the association with underlying breast cancer in 1874.<sup>[4]</sup> In his paper, Paget described 15 women between 40 to 60 years old, who first presented with the skin changes involving nipple-areolar complex, and subsequently progressed to development of breast cancer. He noted that all fifteen patients initially presented with an itching eczema-like rash and discharge from the nipple, which were refractory to common remedies, and within the following year progressed to cancer.

The vast majority of patients diagnosed with Paget's disease have an associated underlying neoplasm in the breast. In several series, the percentage of patients diagnosed with Paget's disease of the nipple found to have invasive or non-invasive carcinoma is upwards of 90%.<sup>[1,5-8]</sup> Up to 50% of the patients with Paget's disease present with a palpable mass in their breast.<sup>[1,6]</sup>

On the microscopic level, Paget's disease is characterized by epidermal invasion by malignant glandular cells, which are large, foamy cells that may contain mucin.<sup>[9,10]</sup> These cells when stained with hematoxylin and eosin have pale cytoplasm and hyperchromatic nuclei.<sup>[11]</sup> In more advanced disease keratinocytes with atypia and epidermal hyperplasia are not uncommon. Some cells might also contain melanin in their cytoplasm.<sup>[12]</sup>

Expert group of oncologist meet in the update in oncology-X-2017 to discuss on recent updates in diagnosis tools and treatment option for Paget's disease in Breast cancer.

The update in oncology-X-2017 was organized by Sir Ganga Ram Hospital group met to discuss and arrive at a consensus statement to provide community oncologists practical guidelines for challenging common case scenarios in Breast Cancer out of these we are discuss about Paget's disease in Breast cancer

in this chapter. While the discussions will take the scenario as exists in India as a representative country with limited resources, the final manuscript is applicable globally.<sup>[13,14]</sup> The discussion was based on domain expertise of the National as well as international faculty, published evidence and practical experience in real life management of breast cancer patients. Opinion of the 250 oncologist including medical oncologist, radiation oncologist, surgical oncologist, molecular oncologist and radiologist are present in the update in oncology-X-2017 was taken into consideration by the expert panel. The expert group was chaired by Dr. Vijay Arora whereas the discussions were moderated by Dr. Gaurav Agarwal.

The core expert group consists Dr. Vivek Gupta, Dr. Rakesh Koul, Dr. S. Dabas, Dr. Ramesh Sareen, and Dr. K. Geeta. Consensus answers were used as the basis of formulating the consensus statement providing community oncologists with ready-to-use practical recommendations. The survey answers were used as the basis for formulating the consensus statement so that community oncologists have a ready-to-use Paget's disease in Breast cancer.

As part of the background work, the best existing evidence was compiled and provided to the expert group panel members for review in preparation of the expert group meeting.<sup>[15-17]</sup> The national and international experts invited to this meeting were also provided the data on the voting by the audience delegates from the update in oncology-X-2017. Members of the panel were also allowed to share their personal experiences, make comments and record dissent while voting for the consensus statements. Total of Six broad question categories were part of the expert group discussions [Tables 1-9].

## Clinical Features

The clinical appearance of the Paget's disease is usually a thickened, sometimes pigmented, eczematoid, erythematous weeping or crusted lesion with irregular borders. The surface of the lesion is occasionally slightly infiltrated. Complaints of pain or itching are frequent. The nipple may be retracted or deformed. Early changes including scaling and redness may be mistaken for eczema or some other inflammatory conditions.<sup>[18,19]</sup> The inflammatory component may be improved by topical treatment, a result that masks the underlying condition and this may cause delay in diagnosis.<sup>[18]</sup> These stages

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**Table 1: Question categories addressed by the update in oncology-X-2017**

Broad question title
Case - A middle aged women presented with itching, discharge and superficial ulceration of left NAC. She got evaluated by the oncologist who on examination confirmed the findings along with the partially eroded nipple. There was no associated palpable lump in the breast? Question 1 - The most preferred method of histological diagnosis will be? Question 2 - Histopathology was consistent with Pagets' disease; Breast mammogram did not reveal any breast lesion Is MR mammogram indicated? Question 3 - What can be the best possible treatment option?
Case 2 - In other scenario there was an associated, solitary lump, size 2.5 cm × 2.0 cm, found on imaging in retroareolar region of the same breast Core needle biopsy of the lump was s/o low grade DCIS and full thickness biopsy of NAC revealed Pagets' disease? Question 4 - The preferred choice of surgical treatment will be? Question 5 - Postbreast conservation surgery if contemplated in this case, should radiotherapy be considered in adjuvant setting? Question 6 - Can she be considered for lumpectomy without lymph node biopsy followed by APBI?
Two additional questions on the controversial topics added by the moderators on which the expert panel gave their consensus Question 7 - What biomarkers should be done in above case? Question 8 - What is role of hormonal treatment in above case?

MR=Magnetic resonance, NAC=Nipple-areola complex, DCIS=Ductal carcinoma *in situ*

**Table 2: Question 1 - The most preferred method of histological diagnosis will be?**

Options (%)	Cytology of the discharge	Shave biopsy of the epidermis	Punch biopsy	Wedge biopsy
Percentage of polled oncologists	33.3	0	22.2	44.4

Expert group consensus: Expert panel recommended wedge biopsy

**Table 3: Question 2 - Histopathology was consistent with Pagets' disease; breast mammogram did not reveal any breast lesion. Is magnetic resonance mammogram indicated?**

Options (%)	Yes	No
Percentage of polled oncologists	77	33

Expert group consensus: Expert panel recommended MR mammography as option in cases where mammography is unhelpful. MR=Magnetic resonance

of the Paget's disease may result in ulceration, destruction of the nipple-areola complex<sup>[19]</sup> and bloody discharge. The lesions are almost unilateral and very rarely bilateral.<sup>[20]</sup> Paget's disease may also develop on ectopic breasts<sup>[21]</sup> and accessory nipples.<sup>[22]</sup> No clinical and epidemiologic factors are known to predispose patients to develop Paget's disease.

## Diagnosis

The diagnosis of Paget's disease can be made from a wedge biopsy, a superficial "shave" biopsy of epidermis or punch biopsy. The wedge biopsy is the most useful method to make the diagnosis because the epidermis can adequately represent and the biopsy is likely to include a part of lactiferous duct. The shave biopsy is less likely to contain sufficient number of Paget's cells, especially when the surface of the lesion is ulcerated. Although a punch biopsy will include the underlying

stroma and possibly part of a duct, there is frequently little epidermis to examine. None of these procedures are always successful; therefore, it is sometimes necessary to take a second biopsy or excise the nipple.<sup>[19]</sup> When a patient has nipple-areola skin changes, a full thickness biopsy of the nipple and areola is important to establish the diagnosis. The use of immunohistochemical stainings, such as carcinoembryonic antigen (CEA), mucin or Her-2 oncoprotein, has been suggested to enhance the diagnosis;<sup>[23]</sup> however, a negative result does not exclude a diagnosis of Paget's disease of the breast, and therefore open (surgical) biopsy should be considered as standard for the diagnosis of Paget's disease of the breast.

The diagnosis of Paget's disease is generally made on the basis of clinical findings. However, when the signs are evident and Paget's disease is suspected, imaging should be performed to detect the underlying carcinoma. Radiologic findings are important to assess appropriate further management and the treatment of the disease. Conventional imaging modalities such as mammography (MMG) may depict a mass or calcification representative of invasive cancer or DCIS, respectively. However, MMG is not always a reliable procedure for detecting MPD. It is limited in its depiction of underlying DCIS in women with Paget's disease.<sup>[24]</sup>

Magnetic resonance imaging (MRI) is known to be highly sensitive for the detection of breast cancer, especially in patients whose mammographic or USG findings are normal or the extent of disease is uncertain.<sup>[25,26]</sup> MRI may show abnormal nipple enhancement, thickening of the nipple-areola complex, an associated enhancing DCIS or invasive tumor, or a combination of these, even when clinically unsuspected.<sup>[27,28]</sup>

Because mammography have limitations in the evaluation of patients with Paget's disease, in the setting of clinically and mammographically occult disease, additional evaluation with MRI can help detect underlying invasive cancer and DCIS. Additionally, MRI may have a role in the preoperative evaluation of the patient and might facilitate appropriate further treatment decisions. In fact, if the diagnosis is based solely on radiologic findings without careful clinical examination, it may result in a delay in diagnosis. As a result, both clinical and imaging findings are complementary and should be correlated to confirm or exclude a diagnosis of Paget's disease.

## Pathogenesis of Paget's Disease

Two theories have been proposed in regards to pathogenesis of Paget's disease: (I) epidermotropic theory and (II) *in situ* malignant transformation theory. The first theory claims that changes typical for Paget's disease arise in the ductal cells, and spread along the basement membrane to the nipple.<sup>[29]</sup> This theory is supported by the fact that most patients with Paget's have underlying breast cancer, and the cells from the nipple are histologically similar to the associated invasive carcinoma.<sup>[30]</sup> The *in situ* malignant transformation theory claim holds that Paget's disease originates in the epidermal cells of the nipple by malignant transformation of keratinocytes and is not associated with any coexisting neoplastic process in the affected breast.<sup>[8,31]</sup>

## Treatment

The surgical treatment of Paget's disease is controversial. Mastectomy with or without axillary lymph node dissection has

**Table 4: Question 3 - What can be the best possible treatment option?**

Options (%)	Wide local excision, including NAC with whole breast irradiation therapy	Total mastectomy±SNB with or without reconstruction	Wide local excision, including NAC±SNB without radiation therapy
Percentage of polled oncologists	60	0	40

Expert group consensus: Expert panel recommend for wide local excision followed by radiotherapy. NAC=Nipple-areola complex, SNB=Sentinel node biopsy

**Table 5: Question 4 - The preferred choice of surgical treatment will be?**

Options (%)	Breast conservation surgery with or without SLNB	Mastectomy with or without SLNB
Percentage of polled oncologists	92.3	7.7

Expert group consensus: Breast conservation surgery with or without SLNB. SLNB=Sentinel lymph node biopsy

**Table 6: Question 5 - Postbreast conservation surgery if contemplated in this case, should radiotherapy be considered in adjuvant setting?**

Options (%)	Yes	No
Percentage of polled oncologists	93.3	6.4

Expert group consensus: Expert panel recommended giving radiotherapy in adjuvant setting

**Table 7: Question 6 - Can she be considered for lumpectomy without lymph node biopsy followed by APBI?**

Options (%)	Yes	No
Percentage of polled oncologists	64.3	35.7

Expert group consensus: Expert panel recommended lumpectomy followed by APBI if lymph node biopsy is not done

**Table 8: Question 7 - What biomarkers should be done in above case?**

Expert group consensus: Biomarkers to be done include ER, PR and HER 2/neu

ER=Estrogen receptor, PR=Progesterone receptor, HER 2=Human epidermal growth factor receptor 2

**Table 9: Role of hormonal treatment in above case?**

Expert group consensus: If histology confirms DCIS plus ER and/or PR is positive, hormonal treatment is recommended

DCIS=Ductal carcinoma *in situ*, ER=Estrogen receptor, PR=Progesterone receptor

long been regarded as the standard therapy for Paget's disease, even in the absence of other clinical signs of malignancy.<sup>[31]</sup> The underlying mass is often invasive cancer with a high risk of axillary node metastases. The patients have a poorer prognosis and usually the appropriate therapy is based on the pathologic findings of the mass and axillary staging.<sup>[32]</sup> In the literature, almost all patients treated with local excision, radiotherapy, or both had the clinical presentation of Paget's disease without a palpable mass. Dixon *et al.* reported a high recurrence rate of 40% in patients treated with local excision alone, whose mammograms suggested *in situ* changes confined to the nipple area.<sup>[33]</sup> Polgár *et al.* reported a local recurrence rate of 33% with a median follow-up time of 6 years in 33 patients treated with local excision alone with or without underlying ductal carcinoma *in situ* confined to the nipple-areola complex.<sup>[34]</sup> They concluded that the local excision alone was not an appropriate treatment for patients with Paget's disease of the nipple.

With the increasing diagnosis of the early breast cancers and the findings from multiple randomized, prospective South Asian Journal of Cancer ♦ Volume 7 ♦ Issue 2 ♦ April-June 2018

trials demonstrating that breast conserving therapy is a feasible alternative for patients with disease limited to the central segment of the breast,<sup>[35,36]</sup> the reported techniques for conservative management of Paget's disease vary widely. These include nipple excision alone (partial or complete), central segmentectomy alone, these resections plus radiation and radiation without resection.<sup>[33,37,38]</sup> Recent reports from several studies with long-term follow-up have shown that breast-conserving surgery is equivalent to mastectomy in terms of overall and disease-free survival in patients with breast cancer.<sup>[39-41]</sup> If conservative therapy is adopted, the patient should be followed up carefully with regular mammography.<sup>[42]</sup> Mastectomy should be reserved for the few occasions, when relapse occurs.<sup>[38]</sup>

Use of breast radiation therapy alone for the Paget's disease of the breast has been reported in limited numbers and with varying results.<sup>[37,38,43]</sup> Current studies suggest that irradiation of the breast tissue to a radical dose may be effective against DCIS.<sup>[44]</sup> This gives support to the view that selected patients with Paget's disease of the breast can be treated by radiotherapy as an alternative to radical surgery in selected patients with Paget's disease confined to the nipple, without clinical or radiological detectable breast tumor.<sup>[43]</sup>

## Conclusion

Paget's disease of the breast is a relatively uncommon condition affecting the nipple and the surrounding tissue. Almost universally, it is associated with DCIS or invasive cancer in the ipsilateral breast. Because these underlying malignancies tend to be multifocal and multicentric, mammography often is not sufficient and MRI may be necessary to evaluate the true extent of the disease. Both total mastectomy and breast preserving surgery followed by appropriate adjuvant therapy are acceptable treatment options for carefully selected patients with Paget's disease. The output of this discussion is to provide the best and effective method of diagnosis of disease and provide best treatment options for patients with Paget's disease of the breast cancer.

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## Conflicts of interest

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