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## Encysted Papillary Carcinoma of the Breast (EPC): A Follow-up Study to Investigate the Role of Sentinel Lymph Node Biopsy

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## ABSTRACT

**Background:** Encysted papillary carcinoma (EPC) is a rare breast neoplasm that mainly affects postmenopausal women. The purpose of this study was to examine whether a sentinel node biopsy would be deemed necessary in patients with a diagnosis of EPC and to determine if evidence of invasiveness can be diagnosed on a core needle biopsy with sufficient confidence to guide decision making for upfront axillary SLNB.

**Methods:** The available data of patients with EPC of the breast were reviewed at a tertiary breast cancer unit over a period of 10 years (2009-2019) and the concordance between core needle biopsy and final histology was assessed. We also carried out a detailed review of the available literature to inform best practice guidance for management of the axilla.

**Results:** During the study, a total of 37 EPC patients were identified, of whom 10 were excluded as they declined further treatment, providing us a study sample of 27 patients. The median age at diagnosis was 72 years (range 47-97) and the vast majority of patients (96%) were Estrogen Receptor (ER) positive. Of the 27 patients treated, 17 (63%) underwent a diagnostic axillary Sentinel Lymph Node Biopsy (SLNB). On the final histology, 13/27 (48%) proved to have invasive disease. A total of 5 (18%) patients had evidence of metastasis in the axillary nodes, of whom only 7% had macro-metastatic disease that warranted further axillary treatment. None of the treated patients had evidence of recurrence or distant metastatic disease, to date (median of 5 years of follow up).

**Conclusion:** Encysted papillary carcinoma is associated with a low incidence of axillary node involvement. SLNB should only be carried out when there is evidence of invasive cancer. An algorithm was developed to help guide management of the axilla in cases diagnosed with EPC on diagnostic core needle biopsy.

### Introduction

Encysted papillary carcinoma (EPC) of the breast is a rare breast cancer subtype. It is characterised by a papillary carcinoma which is located within a well-circumscribed cystic or distended mammary duct. It

accounts for less than 3% of all cases of breast cancer and typically occurs in postmenopausal women.<sup>1, 2</sup> EPC is also described as encapsulated or intra cystic papillary carcinoma. In the literature, it has been considered as a variant of Ductal Carcinoma in-Situ (DCIS), given its discrete nodular growth, its lack of stromal reaction, as well as its indolent clinical behaviour.<sup>3, 4</sup> However, unlike classic DCIS, EPCs lack myoepithelial cells which, in many cases, can lead to the conclusion that some EPCs are, in fact, invasive carcinomas with an expansile growth pattern (Figures 1a & 1b).<sup>5</sup> The latter hypothesis is further

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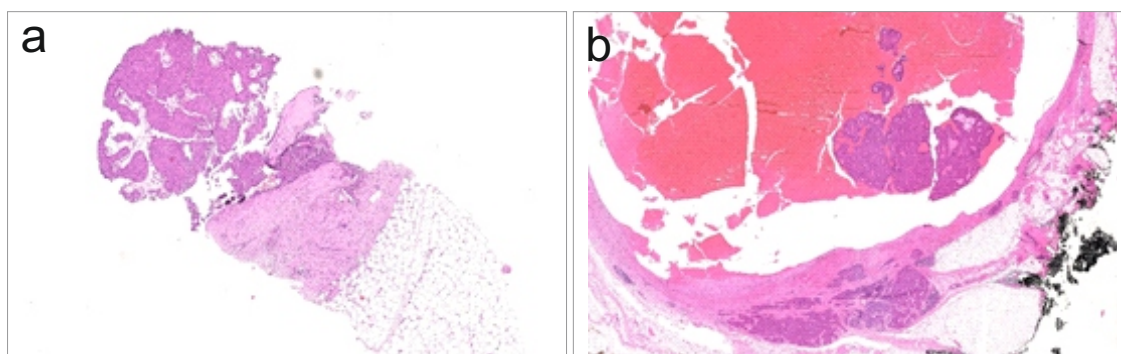
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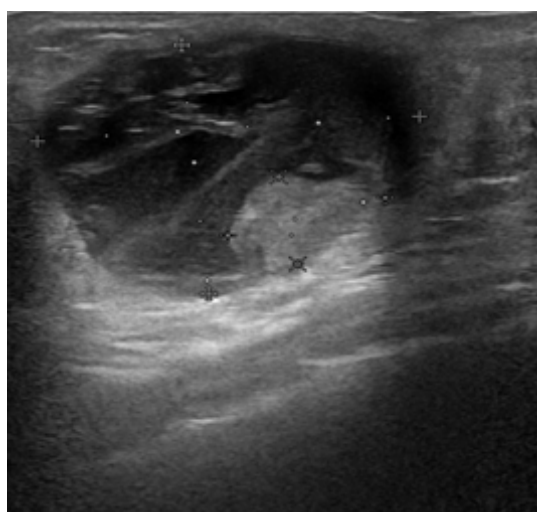


**Figures 1a & 1b.** Breast core biopsy (a) and wide local excision (b) of EPC (Hematoxylin and Eosin stain original magnification x 40). Core biopsy revealed an intermediate grade EPC. Final histology of the same patient revealed a Grade 2 invasive carcinoma of No Special Type (NST) adjacent to the EPC.

substantiated by their ability to metastasise to axillary lymph nodes in a small number of cases and the even rarer occurrence of distant metastatic disease.<sup>1</sup>

In 2012, the WHO working group acknowledged the potential of minimal invasion in these non-aggressive lesions. However, despite the lack of myoepithelial cells around these lesions, EPC is referred to as an in-situ disease for the purposes of staging. However, there is no consensus on how to stage EPC in available literature and therefore unsurprisingly there is a lack of agreement on how to manage it.<sup>6</sup>

Encysted papillary carcinoma presents most commonly as a palpable lump in 70-80% of cases, nipple discharge, or then as an incidental finding on breast imaging. It appears as a lobulated or well circumscribed lesion on mammogram or as a complex cyst with vascular flow on ultrasound (Figure 2).<sup>7</sup> Almost 50% of EPCs have been identified in the retro-areolar region.<sup>8</sup> Traditionally, patients diagnosed with EPCs have good prognosis in both in situ and invasive subgroups. They are slow



**Figure 2.** Breast ultrasound image showing a mixed echogenic lesion [solid component (arrow) within a well circumscribed cystic lesion]. Cytology of fluid aspirate revealed atypical cells suspicious of malignancy. A core biopsy of the residual solid component revealed a papillary lesion with atypia, highly suggestive of an EPC.

growing tumours with a 10-year survival rate of 100% and a disease-free survival rate of 91%.<sup>9,10</sup>

Recent data have demonstrated significant discrepancies in the management of the axilla following diagnosis of EPC. The largest study to date, based on the SEER database (total of 2649 patients, from 2000 to 2009), and published in 2016, showed a 5.5% incidence of axillary lymph node involvement in all EPCs. Therefore, a sentinel lymph node biopsy (SLNB) was recommended for all patients with EPC, as the node positive patient cohort possessed the worse overall prognosis.<sup>11</sup> Another study from Nottingham (302 Papillary Carcinomas, including 208 EPCs, from 1990 to 2010), published in 2011 demonstrated that 3% of patients with EPC had evidence of micro-metastatic disease in the axillary nodes. This study suggested that management of axillary lymph nodes in EPCs should be similar to that of conventional DCIS, where synchronous SLNB should only be performed along with a mastectomy or in cases with evidence of invasive disease on final histology, following breast conserving surgery.<sup>12</sup> Another review of 917 patients between 1988 and 2005 from the California Cancer Registry (CCR), published in 2008 showed a less than 8% incidence of axillary lymph node involvement and therefore, recommended SLNB for all patients with EPC.<sup>13</sup>

The purpose of this study was to examine whether a sentinel node biopsy would be deemed necessary in patients with a diagnosis of an encysted papillary carcinoma and to determine if evidence of invasiveness can be diagnosed on a core needle biopsy with sufficient confidence to guide decision making for upfront axillary SLNB.

### Methods

The available data of patients diagnosed with EPC of breast were reviewed at a tertiary breast cancer unit over a period of 10 years (2009-2019) and the concordance between core needle biopsy and final histology was assessed. Patients' level data were retrieved from the hospital electronic medical



records. Furthermore, a comprehensive review of the PubMed database (with “encysted papillary carcinoma” as the search term) was performed. Particular consideration was given to the California Cancer Registry review (2008), the SEER database analysis (2016) and the study from the University Nottingham (2011) to determine the appropriate clinical assessment and management of patients with breast EPC.

## Results

Between 2009 and 2019, there were a total of 37 patients diagnosed with EPC of the breast. The median age at diagnosis was 72 years (range 47-97) and the vast majority of patients (96%) were Estrogen Receptor (ER) positive.

In 36 out of 37 patients (96%), EPC was diagnosed in core biopsy. In 1 (4%) patient, the core

biopsy revealed a papillary lesion (B3) that was confirmed as an EPC following an excision biopsy. Overall, 27 patients (73%) underwent treatment and the remaining 10 (17%) were either deemed as very high risk for general anaesthesia due to comorbidities or declined any form of treatment.

Of the 27 patients who received treatment, only 2 (7%) had evidence of invasive disease on their core biopsy. Also 2 (7%) patients had features suspicious for invasion. Consequently, these 4 patients (14%) underwent a synchronous SLNB. Twenty-six (96%) patients were strongly Estrogen Receptor (ER) positive. Twenty-two (81%) of the 27 underwent a Wide Local Excision (WLE) and 5/27 (19%) chose to undergo a mastectomy with synchronous SLNB. A total of 13/27 (48%) treated patients had invasive disease on their final histological specimen and 8/27 (30%) of them had associated DCIS (Table 1).

**Table 1.** Characteristics of treated EPC patients (n=27)

Variabeles		n	(%)
Invasion based on core biopsy	Yes	2	7.4
	No	23	85.2
	Suspicious	2	7.4
Estrogen Receptor (ER)	Positive	26	96.3
	Negative	1	3.7
Type of Breast Surgical Treatment	Breast Conserving Surgery (BCS)	22	81.5
	Mastectomy (MX)	5	18.5
Invasion based on final histology	Yes	13	48.1
	No	14	51.9
Associate DCIS*	Yes	8	29.6
	No	19	70.4
Sentinel Lymph Node Biopsy (SLNB)	Yes	17	63
	No	10	37
		2	7.4
Axillary metastasis	Yes (Macro-metastasis)		
	Yes (Micro-metastasis)	3	11.1
	No	22	81.5
Distant metastasis	Yes	0	0
	No	27	100

\*DCIS: Ductal Carcinoma in Situ

Seventeen (63%) out of the 27 patients underwent a diagnostic SLNB to stage the axilla. This included patients who underwent a diagnostic SLNB at the time of their primary surgery either due to evidence or suspicion of invasive disease on their core biopsy or then due to the fact that they opted for a mastectomy. The remaining patients underwent a diagnostic SLNB following the diagnosis of invasive disease on their final histology. There was a 90 year old lady, who had invasive disease diagnosed on her final histology, but following a multi-disciplinary team discussion a SLNB was not deemed necessary, considering her advanced age, her low risk of recurrence and strong ER positivity. Two (7%) patients had evidence of macro-metastatic disease on SLNB and underwent a subsequent completion axillary clearance (cANC). Three (11%) patients had evidence of micro-metastatic disease in the nodes, which did not warrant

any further surgical intervention based on current breast cancer management guidelines. After a median follow up of 5 years, none of the treated patients developed locoregional recurrence or distant metastases (Table 1).

## Discussion

There are a limited number of published clinical studies on EPC. Most of the studies are case reports or small case series from single institutions.

The perception that EPC is a malignancy of elderly post-menopausal women<sup>1</sup>, was supported by data from the current study, where the median age at diagnosis was 72 years. However, a recent clinical study involving 900 patients showed that 3.5% of them were male patients.<sup>13</sup> The vast majority of published case series on EPC have not included male patients.



There is significant controversy regarding potential invasiveness of EPC and its ability to spread to the axilla. As a consequence, the management of this disease does not conform to agreed guidelines. In general, regardless of the therapeutic surgical strategy, the prognosis of EPC is generally excellent.<sup>12</sup>

The California Cancer Registry (CCR) in a review of 917 cases showed that 7.8% of cases had regional disease, with either direct spread into adjacent tissues or axillary lymph nodes. They failed to specify the exact proportion of patients with micro-metastatic and macro-metastatic axillary nodal disease. The incidence of axillary lymph node involvement, despite being quite low, led to the recommendation to proceed with a diagnostic axillary sentinel lymph node biopsy (SLNB) in all patients with EPC, regardless of the presence of invasive disease within the diagnosed EPC.<sup>13</sup>

In another important study from the Surveillance, Epidemiology, and End Results (SEER) registry including 2,649 female patients with EPC, axillary involvement was a key component. They reported that 5.5% of patients had axillary lymph node involvement. This study also showed that despite the low probability, EPC can spread to the axillary nodes. However, this study failed to clarify whether patients with axillary nodal involvement had largely micro-metastatic or then macro-metastatic disease. Analysis on whether axillary spread occurred in cases of pure EPC or in cases associated with DCIS or lymphovascular space invasion, was also missing. They did underline the significance of the lymph node status in EPC, since all patients with a pathologic negative axilla had a better overall survival rate. Consequently, they recommended that a SLNB should be performed for all patients with a diagnosed EPC.<sup>11</sup>

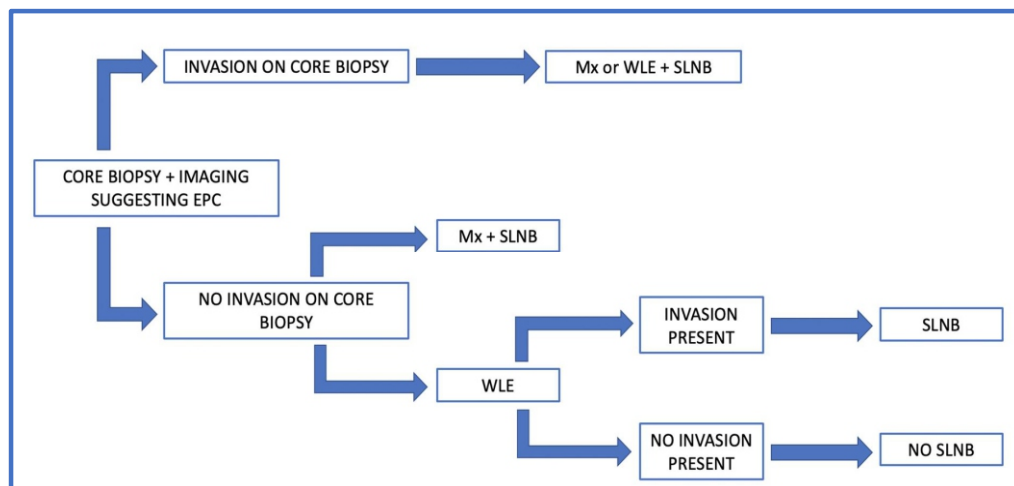
Furthermore, a study of 208 patients, published by the university of Nottingham showed that 3% of cases with EPC had axillary lymph node micro-

metastasis. According to this study, EPC, which is entirely surrounded by a layer of myoepithelial cells is considered an in-situ lesion. They recommended that this histological subtype should be regarded as papillary carcinoma in situ and should be treated similarly to DCIS. Moreover, this important study demonstrated that the outcome of patients with pure EPC or EPC associated with microinvasion or suspicion of invasion are not different, and both have excellent prognosis with local therapy alone.<sup>12</sup>

In a case report published in 2017, a 70 year old female presented with a 120mm mass on ultrasound which on biopsy proved to be an EPC and was treated with a WLE and SLNB showing macrometastasis in one of the two lymph nodes excised. She subsequently underwent ALNC. The final histology of the breast specimen showed encysted papillary carcinoma of pre-dominantly intermediate nuclear pleomorphic grade with no evidence of conventional invasion.<sup>14</sup> A magnetic resonance imaging following the operation showed that there was no other lesion in the breast, proving that the macrometastasis was caused exclusively by the EPC. This article was published as a case report emphasizing the rarity of lymph node metastasis in EPC.

In agreement with our study is a recent review by Wang et al.<sup>15</sup> 99 cases of Papillary carcinoma were evaluated, 43 of whom had EPC. It was proved that in these cases there was minimal lymph node involvement even in tumours with invasive component. The patients' long term survival was outstanding as shown in our current study. This review concluded that there is no indication for routine SLNB in patients with papillary carcinoma treated with Wide local excision surgery.

In summary, there is a distinct lack of consensus for performing SLNB in patients with the diagnosis of EPC. The decision of upfront surgery to the axilla should be based on clinical indications guided by the histopathological characteristics of the EPC on core biopsy. These should be balanced against the



**Figure 3.** Treatment algorithm for patients diagnosed with EPC of breast on core biopsy. (Mx: Mastectomy, WLE: Wide Local Excision, SLNB: Sentinel Lymph Node Biopsy)



potential risks and associated morbidity following an axillary intervention, such as upper limb lymphoedema, longstanding shoulder stiffness and significant neurovascular injury. In light of this, we have developed a comprehensive treatment algorithm to help guide axillary surgical interventions and potentially reduced morbidity [Figure 3]. We believe that a synchronous SLNB should not be the intervention of choice in all patients with the diagnosis of EPC. Synchronous SLNB should only be considered in patients with EPC that is associated with unequivocal evidence of invasion or in cases with a high suspicion of invasion. SLNB should also be the appropriate surgical approach in patients undergoing a mastectomy, as their primary breast treatment. Consequently, in the vast majority of patients with EPC and no evidence of invasion on core biopsy, SLNB should not be performed, unless they undergo a mastectomy as opposed to breast conserving surgery (BCS). Finally, in patients undergoing BCS with no proven invasion or suspicion of invasion on core biopsy, SLNB should only be performed as a second standalone diagnostic procedure, when invasion is reported following a wide excision on the breast final histology.

In conclusion, encysted papillary carcinoma is a rare malignant neoplasm of the breast with excellent prognosis that affects older, postmenopausal women. Patients with EPC require Sentinel Lymph Node Biopsy (SLNB) for staging of axilla, only if there is evidence or suspicion of invasion in their core biopsy or final histology specimen or if they are undergoing a mastectomy as their primary treatment. Routine axillary surgery in all cases undergoing BCS should be avoided. Based on our own experience, and a comprehensive review of available evidence, we have proposed an algorithm for the role of SLNB following a diagnosis of EPC.

#### Conflict of Interest

None.

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