International Journal of Research and Review
[Indexed, Peer-Reviewed Journal]
Volume 12; Issue: 6; June 2025
Website: www.ijrrjournal.com
Research Paper *E-ISSN: 2349-9788; P-ISSN: 2454-2237*

Encapsulated Papillary Carcinomas of Breast, The Enigmatic Lesions

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DOI: https://doi.org/10.52403/ijrr.20250692

ABSTRACT

Encapsulated papillary carcinoma (EPC) is a rare entity among breast malignancies that accounts for < 1- 2 %. Even though they lack distinct myoepithelial layer they are considered as an in-situ carcinomas unless associated with invasive component. Because of overlapping features in benign and malignant conditions, the accurate subcategorization of these lesions is difficult despite of the papillary architecture, commonly leading to misdiagnosis and improper treatment. EPC is a slowly growing tumor with a thick peripheral fibrous capsule and proliferating cell structure with a supporting fibrovascular stalk. It is a unique tumor with the characteristic feature of myoepithelial layer absence both in capsule and in the papillae. Materials and Methods: A retrospective analysis of all the cases reported as encapsulated papillary carcinomas in the department of pathology over a period of 5 years was done. The H & E-stained slides were reviewed based on architectural features along with detailed clinical history. Histological grading was done. Immunohistochemical staining was done to visualize the presence or absence of myoepithelial layer. ER, PR and HER2/neu staining was done to find out the hormonal status of the tumor. Results: The total number of breast lesions were 288 over a period of 5 years. Among them 62 (21.5%) were breast malignancies. Six cases (10 %) out of 62 breast malignancies were encapsulated papillary carcinomas. Forty-three (15%) out of total breast lesions (288) were Papillary neoplasms. Of the 43 papillary lesions 14% were encapsulated papillary carcinomas. The average age of patients in encapsulated papillary carcinomas was 47 years. The average tumor size was 2.2 cms. Five cases (84%) were of histological grade 1 and 1 case (16%) showed grade 2. Myoepithelial layer was absent in all the 6 cases (100%). Of the 6 cases, 5 patients were positive for hormonal receptors (ER and PR) and negative for HER2/neu. Only 1 case (16%) with invasion showed negative for all receptors. Conclusion: Encapsulated papillary carcinomas need to be thoroughly investigated for nuclear grade and invasion in order to avoid over treatment. In the absence of invasion encapsulated papillary carcinomas have very good prognosis.

Keywords: Encapsulated, papillary, breast, grade, myoepithelial layer, invasion, in situ, prognosis, hormone receptors.

INTRODUCTION

Among breast malignancies, encapsulated papillary carcinoma (EPC) is a rare entity that accounts for <1-2% of breast malignancies, it is considered as an in-situ carcinoma even though it lacks distinct myoepithelial layer unless associated with

invasive component (1,2). These Papillary lesions are heterogeneous, with different biological patterns, identical clinical behavior and histomorphological features (3). The accurate subcategorization of these lesions is difficult because of overlapping features in benign and malignant conditions, despite of the papillary architecture, commonly leading to misdiagnosis and improper treatment (4,5). World health organization (WHO 2019) classified papillary neoplasms of breast into five subtypes, they are Intraductal papilloma, Papillary ductal carcinoma in situ, Encapsulated papillary carcinoma, Solid-papillary carcinoma and Invasive papillary carcinoma (3). EPC is a slowly growing tumor and histologically it is a unique malignancy characterized by thick peripheral fibrous capsule and proliferating cell structure with a supporting fibrovascular stalk. Myoepithelial layer is absent both in capsule and in the papillae which is the characteristic feature of EPC (6,7).

AIMS AND OBJECTIVES:

The aim of the study is to evaluate the histomorphological features, study the hormonal status, diagnostic pitfalls and prognostication of Encapsulated papillary carcinomas.

MATERIALS & METHODS

A retrospective analysis of all the cases reported as encapsulated papillary carcinomas in the department of pathology over a period of 5 years (i.e. from June 2018 to May 2023) was done. The H & E-stained slides were reviewed based on architectural features along with detailed clinical history. Histological grading was done according to Nottingham scoring. Immunohistochemical staining was done to visualize the presence or absence of myoepithelial layer. ER, PR and HER2/neu staining was done to find out the hormonal status of the tumor.

STATISTICAL ANALYSIS

The data was entered in the excel spread sheet and the results were expressed as frequencies and percentages for comparisons.

RESULT

The total number of breast lesions were 288 over a period of 5 years. Among them 62 (21.5%) were breast malignancies (Table 1). Six (10 %) out of 62 breast malignancies were encapsulated papillary carcinomas.

Table- 1: Frequency of breast carcinomas

Carcinoma type	Frequency (n=62)	Percent (%)
Invasive ductal carcinoma	34	55
Invasive lobular carcinoma	08	13
Encapsulated papillary carcinoma	06	10
Invasive breast carcinoma with medullary pattern	05	8
Invasive micropapillary carcinoma	03	5
Metaplastic carcinoma	02	3
Mucinous adenocarcinoma	02	3
Epithelial myoepithelial carcinoma	01	1.5
Secretory carcinoma	01	1.5
Total	62	100

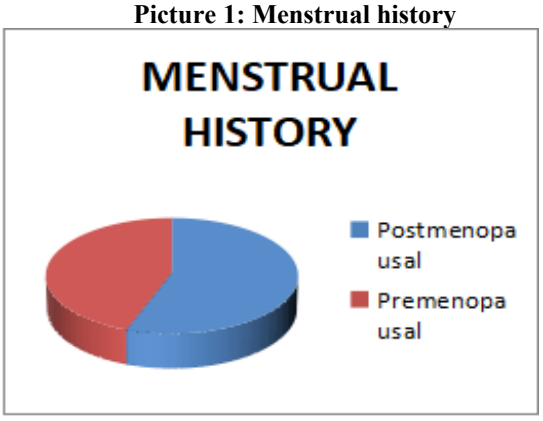
Forty-three (15%) out of total breast lesions (288) were Papillary neoplasms (Table 2). Of the 43 papillary lesions 14% were encapsulated papillary carcinomas.

Table-2: Frequency of Papillary lesions of breast

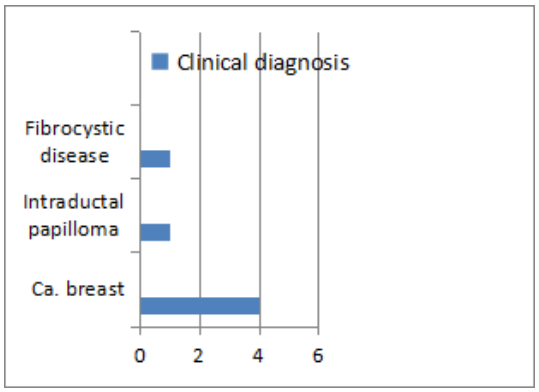
Variable	Frequency (n= 43)	Percentage (%)
Papilloma without atypia	28	65%
Papilloma with ADH/DCIS	04	09%
Encapsulated papillary carcinomas	06	14%
Invasive micropapillary carcinomas	03	07%
Solid papillary carcinoma with invasion	02	05%

The average age of patients in encapsulated papillary carcinomas was 47 years (ranging from 39 to 61) and 4 (66%) were postmenopausal patients (Picture 1). All the cases had no previous history of breast disease or malignancies and no palpable axillary nodes. The clinical diagnosis was breast carcinoma (66%) in 4 patients (Picture: 2). Intraductal papilloma and fibrocystic disease in other two cases.

Picture 1: Menstrual history



Picture 2: Clinical diagnosis



The average tumor size was 2.2 cms. Five cases (84%) were of histological grade 1 and 1 case (16%) showed grade 2. Myoepithelial layer was absent in all the 6 cases (100%). Of the 6 cases, 5 patients were positive for hormonal receptors (ER and PR) and negative for HER2/neu. Only 1 case (16%) with invasion showed negative for all receptors and received chemotherapy. Two patients received hormonal therapy (Table 3).

Table -3: Encapsulated papillary carcinomas

Variables	**Case 1**	**2**	**3**	**4**	**5**	**6**
Duration	1 yr	3 m	1m	2m	6m	NA
Size (cms)	2.5 x 2.0	2.8 x 2.0	2.2 x 2.0	1.1 x 1	1.7 x 1.3	3.0 x 2.3
Site	R.U. Q	L.UOQ	L.UOQ	R.UOQ	L.CQ	L.UQ
Age (years)	36	39	61	48	55	46
Menstrual History	Pre. Meno	Pre. meno	Post. Meno	Post. Meno	Post. Meno	Post Meno
Clinical Diagnosis	Ca. breast	Ca. breast	Ca. breast	Intraductal papilloma	Fibrocystic disease	Ca. breast
Surgery	MRM	MRM	MRM	lumpectomy	Lumpectomy	MRM
In situ component	DCIS	DCIS	-	DCIS	DCIS	-
Invasion	Absent	Absent	Absent	Absent	Absent	Present
Histological grading	1	1	1	1	1	2
LN metastasis	No	No	No	NA	NA	No
ER, PR	Positive	Positive	Positive	Positive	Positive	Negative
HER2/neu	Negative	Negative	Negative	Negative	Negative	Negative
IHC for Myoepithelial layer	Absent SMA negative	Absent SMA negative	Absent S100 negative	Absent S 100 negative	Absent SMA negative	Absent SMA negative

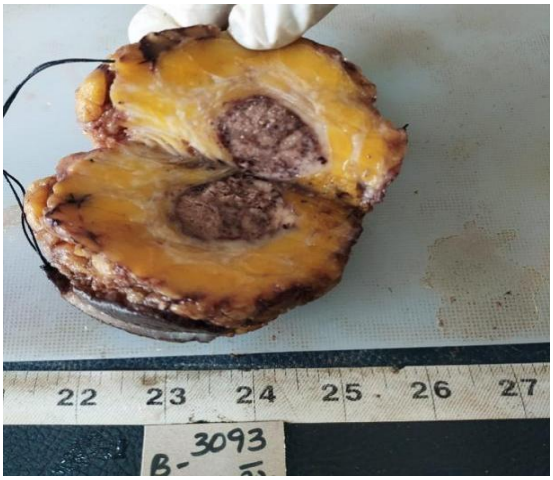
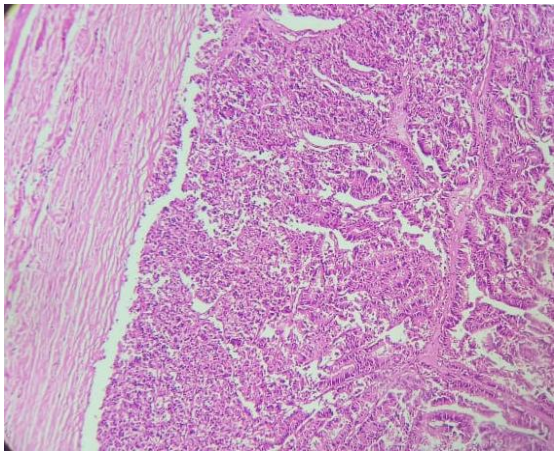


Fig 1a: Gross pictures; Cut section of breast showing cystic area filled with grey white lesion. Fig 1b: Cut section of breast with tumor tissue showing Papillary excrescences.



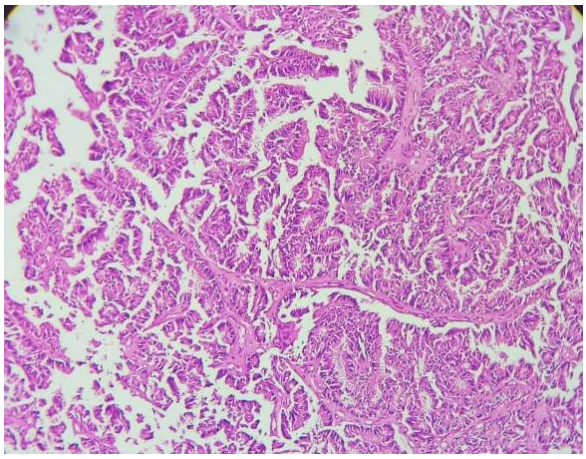
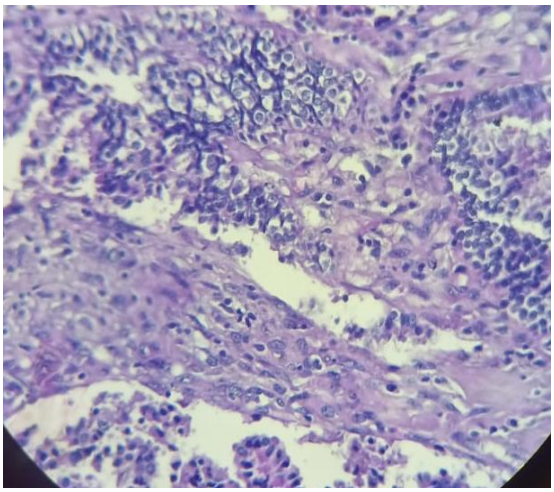


Fig 2a: Microscopy; Thick fibrous capsule surrounding tumor tissue (H & E, X100).
Fig 2b: Tumor tissue arranged in papillary pattern around a central fibrovascular core (H & E, X400).



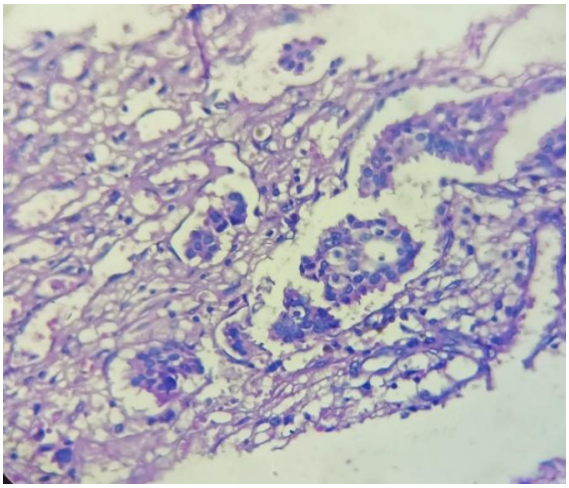


Fig 3a and 3b: Microscopy; Encapsulated papillary carcinoma with areas of invasion (H & E, X100, X400).

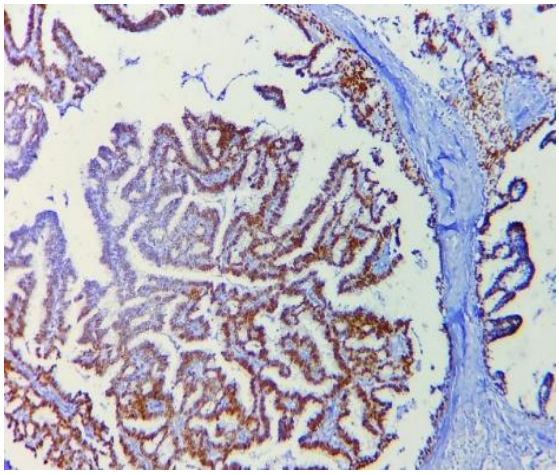
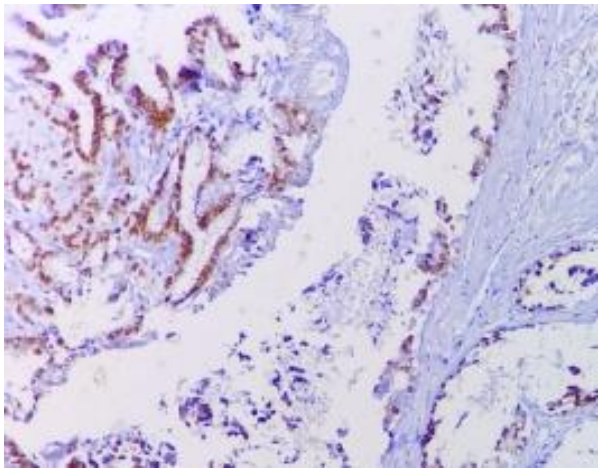



Fig 4a and 4b: Microscopy of tumor cells showing ER and PR positivity (IHC,X100)

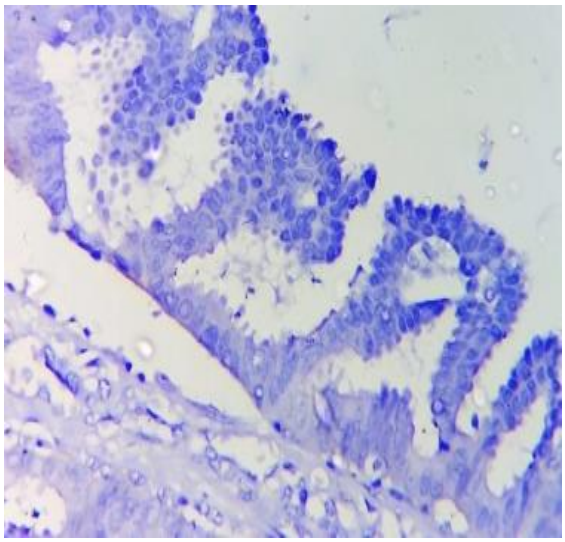
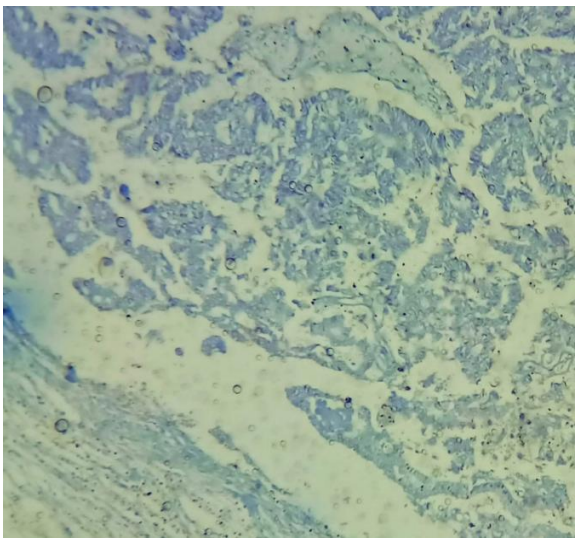



Fig 5a: Tumor cells showing HER2/neu negativity (IHC; X400). Fig 5b: SMA staining showed absence of myoepithelial layer both in the capsule and papillae (IHC; X100).

DISCUSSION

Encapsulated papillary carcinomas are more commonly encountered in post-menopausal women. Occurrence of EPC in young women and men are rare (2). In the study done by Hashmi AA et all the mean age of the EPC patients was 51 years, with a mean tumor size of 2.97±2.46 cms (1). In the present study the mean age of patients was 47 years. EPC's usually remain indolent for many years before diagnosis as they present as painless breast lumps (8). The mean size of encapsulated papillary carcinoma was usually 20 mm, which was similar to the present study (22mm) (9). The sole lesion of encapsulated papillary carcinoma lies inside a cyst (2). Malignancy is usually suspected when there is both solid and cystic components. This solid and cystic nature makes it difficult to diagnose pre-operatively with needle biopsy. There is no clear agreement among different studies whether encapsulated papillary carcinomas are in situ or invasive malignancies. In spite of few reported cases, still there is sparsity of data on the clinicopathological features of EPC's. Also there are EPC's showing high grade with aggressive histological features and clinical behavior (10).

WHO classified (2019) encapsulated papillary carcinomas as invasive and non-invasive types. Invasion is considered when the neoplastic cells invade the stroma, crossing the fibrous capsule. 28.6% - 70% shows ductal carcinoma in situ (DCIS) component in the adjacent breast tissue (3).

Few studies consider encapsulated papillary carcinoma as a variant of DCIS (2). On the other hand, it is also considered as a slowly growing form of invasive carcinoma with expansive potential in view of myoepithelial cell absence (3). Most of the expert's place EPC in between intraductal carcinoma in situ and invasive intraductal carcinoma. In the papillary carcinomas, the lesions are defined as in situ rather than invasive if the myoepithelial cell layer is present at periphery of the nests (2).

Encapsulated papillary carcinomas exhibited invasion associated markers like matrix metalloproteinases, E-cadherin, vascular endothelial growth factor (VEGF) and transforming growth factor receptor-beta to a lesser degree compared to Infiltrative Ductal Carcinoma in a study conducted to assess invasive potential of the tumor. Unless associated with an invasive component outside the tumor capsule, encapsulated papillary carcinomas are staged as in situ carcinomas despite of their invasive potential (1).

According to Hill and Yeh, the continuum of progression between DCIS and invasive disease was identified by the differences in basal membrane endothelial cell staining of intraductal lesions. The expression of invasive proteins like MMP-1 and MMP-9 in encapsulated papillary carcinomas is higher than the DCIS, where as there is no statistically significant difference noted between EPC and invasive carcinomas. The expression of MMP-2 and MMP-7 is higher in invasive carcinomas compared to EPC and DCIS, and their expression is similar in both EPC and DCIS (11,12). Also, lymph node and lung metastasis in pure EPC's indicate their potential to turn into invasive carcinomas in spite of having indolent clinical behavior (13). Encapsulated papillary carcinomas can also mimic an invasive carcinoma due to entrapment of breast epithelium along the needle tract after doing core biopsy (10).

Immunohistochemical stains like SMA, CD10, S-100, calponin, CK5/6, and P63 are used as myoepithelial cell markers, in the present study SMA and S-100 were used to confirm the presence of myoepithilial layer (2,6). Immunohistochemistry has very little role in differentiating Invasive and Non-invasive papillary carcinomas. It can only help in the evaluation of benign and atypical papillary neoplasms.

In breast, Papillary lesions are broadly classified into many types based on the 1) location in ductal system, 2) proliferating epithelial cell nature, 3) presence and location of myoepithelial cells and 4) morphology of papillary carcinomas.

Lesions that arise from large ducts present as solitary papillomas, encapsulated papillary carcinomas or solid papillary carcinomas with mass lesion or nipple discharge. Lesions that arise from small ducts (terminal duct lobular units; TDLU) present as multiple papillomas and papillary ductal carcinoma in situ (DCIS) or as calcifications and incidental findings along with other lesions. Based on the nature of epithelial cells, the lesions can be hyperplastic in papilloma and neoplastic in papillary carcinoma. Encapsulated papillary carcinomas and solid papillary carcinomas are differentiated by the presence of neuroendocrine and mucinous changes. Papillary carcinomas are diagnosed as in situ or invasive depending on the degree of cytonuclear atypia. The presence or absence of myoepithelial cells helps in distinguishing benign papillary lesions from the malignant lesions and also helps in identifying various subtypes of malignant papillary lesions. Based on morphology, the encapsulated and solid papillary carcinomas having well circumscribed margins are considered as non-invasive or in situ carcinomas and those having irregular borders, ragged edges and complex jigsaw patterns in solid papillary carcinomas, or areas of stromal invasion in encapsulated papillary carcinomas are considered as invasive lesions.

Hence it is essential to be aware of all the subtypes of papillary neoplasms and their differential diagnosis as these lesions have overlapping features. These rare cases also

need additional diagnostic work up and fallowing of updated guidelines for accurate diagnosis and management (14).

ER, PR, and HER2/neu positivity was noted in 81.3%, 75%, and 12.5% cases respectively, in the study done by Hashmi AA et all. In the present study 84% of the cases showed ER and HER2/neu positivity. Usually Encapsulated papillary carcinomas are of low or intermediate nuclear grade without necrosis and they are strongly positive for ER and negative for HER-2/neu like in our study 1. In the present study 84% of the cases belonged to histological grade 1.

High grade EPC'S are frequently associated with large size, most common in younger age and are usually negative for hormone receptors. Identification of invasive component and high-grade morphology is very important as the treatment and behavior depends on these features. Also, invasive tumors show more frequent lymph node involvement (15). Encapsulated papillary carcinomas are characterized by limited metastasis, lymphovascular invasion and relapse, there by having a very good prognosis 3,1. In the present study only 1 case (16%) with invasion showed negative for ER, PR and HER2/neu receptors (triple negative) and it belonged to histological grade 2. None of the cases showed lymph node metastasis in the present study.

Outcome and follow up:

The 10-year survival rate in encapsulated papillary carcinoma is > 95%. Lefkowitz et al. studied that at 10 years the disease-free survival rate was 91% and survival rate was 100% 6. The survival rate was 93.8 % in the study done by Hashmi AA et al. (1). All 6 patients of our study were followed up and now they are doing good. Complete surgical resection is the common treatment of choice with adjunct sentinel lymph node biopsy to rule out lymph node metastasis (3). Lumpectomies are associated with local recurrence even if the tumor is negative for Ductal carcinoma in situ or Invasive carcinoma in spite of its indolent nature (16). Recurrence is suspected in pure EPC cases, EPCs associated with DCIS and cases with invasion. Hormonal therapy, chemotherapy and radiotherapy can be given based on specific selective criteria (3). In cases with DCIS or invasion, radiotherapy is the treatment of choice. Adjuvant chemotherapy is advised in histologically aggressive tumors. Adjuvant hormone therapy is recommended for young patients with invasive carcinomas, patients having recurrent disease and for those who are not fit for surgery (2,3).

CONCLUSION

Encapsulated papillary carcinomas need to be thoroughly investigated for nuclear grade and invasion in order to avoid over treatment. In the absence of invasion encapsulated papillary carcinomas have very good prognosis.

Declaration by Authors

Ethical Approval: Approved
Acknowledgement: None
Source of Funding: None
Conflict of Interest: No conflicts of interest declared.

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How to cite this article: Recharla Madhuri, Kharidehal Durga, Nandam Mohan Rao, Syam Sundara Rao B, Thejaswini V. Encapsulated papillary carcinomas of breast, the enigmatic lesions. *International Journal of Research and Review*. 2025; 12(6): 820-827. DOI: *https://doi.org/10.52403/ijrr.20250692*

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