Encapsulated Papillary Carcinoma of the Breast: Clinicopathological Features and Management: Could Sentinel Lymph Node Biopsy Be Exempted?

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Abstract

Background

Any papillary lesion in the breast presents a diagnostic and therapeutic challenge. Encapsulated papillary carcinoma (EPC) is one of the rare types of breast cancer. Evidence-based guidelines are sparse. For this reason, there is no complete clarity in the diagnosis and treatment management, and there are not enough studies in the literature. This study aims to examine the necessity of sentinel lymph node sampling in the management of ECP in line with the patients’ clinicopathological data.

Methods

We retrospectively screened with EPC in our clinic between January 2012 and March 2022. We recorded and statistically evaluated the patients' demographic, clinical, radiological, pathological, and treatment management.

Results

Sixty four EPC patients were identified. The final pathologic evaluation revealed that 19 patients (18.7%) had pure EPC, 27 patients (43.7%) had EPC with associated DCIS, and 18 patients (37.5%) had EPC associated with invasion. The mean age was 61, and 2 patients were male. Breast-conserving surgery was performed in 62 patients, and simple mastectomy was performed in 2. SLNB was found to be positive in only 1 of the patients. Sixty-three patients with EPC were hormone receptor-positive, one patient was triple negative, and they were associated with invasion. No death was in any patient; one had local recurrence, and a mastectomy was performed.

Conclusions

The overall prognosis and long-term survival of EPC is excellent. Our study and current literature indicate routine SLNB is overtreatment since surgical excision with negative margins is sufficient in EPC cases, and lymph node metastasis is rare, even with an invasive component.

Introduction

Encapsulated papillary carcinoma (EPC) of the breast is a rare malignant tumor that accounts for less than 2% of all breast carcinomas in women and is frequently seen in postmenopausal women [1]. There need to be more guidelines in diagnosing and treating this unusual but distinct histological subtype of papillary carcinoma (PC). First, Carter et al. EPC, one of the two forms of non-invasive papillary carcinomas, is currently a neoplasm with a relatively poor prognosis, characterized by both ductal carcinoma in situ (DCIS) and invasive ductal carcinoma (IDC) [2, 3]. Studies have shown that
histologically, the tumor is cystic in a dilated canal by arborization of the fibrovascular stroma and contains papillary cancer nodules surrounded by a thick fibrous capsule [4]. For this reason, some researchers have defined it as encapsulated papillary cancer [5].

Due to the rarity of EPC and the small number of case series, a complete algorithm has yet to be developed to diagnose and treat it. However, the consensus is that EPC is a disease with an excellent prognosis when given adequate excision with negative margins first and is behavior consistent with ductal carcinoma in situ[6]. Since the results of needle aspiration or tru-cut biopsy performed in these patients are generally suspicious, an excisional biopsy is often needed for the diagnosis.

This study aims to shed more light on the clinical presentation, current management practices, and oncologic outcomes of EPC patients treated at our center and to discuss the necessity of radiological imaging and biopsy techniques. Although SLNB is a minimally invasive procedure, it still carries a definite risk of side effects [7, 8]. Therefore, whether SLNB for axillary staging is necessary for these patients is debatable.

**Patients and Methods**

**Patient Cohort**

The Board of Ethics Committee of Mersin University approval was obtained prior to the commencement of this retrospective study. The surgical and pathology databases at Mersin University Hospital were queried from January 2012 to March 2022 to identify all patients with a diagnosis of breast EPC. Sixty-nine patients were identified, and 64 were considered evaluable after five patients were excluded from analysis due to lack of follow-up data. Among the screened breast cancer patients, the cases whose final pathology results were reported as encapsulated papillary cancer (EPC) and its variants were included in the study. Those with EPC variants were defined as those with pure encapsulated papillary cancer (PURE-EPC), those associated with ductal carcinoma in situ (DCIS-EPC), and those with invasive carcinoma associated (INV-EPC).

At the time of diagnosis, the patient's complaints at admission, age, gender, menopausal status, family history, physical examination findings, USG, mammography, localization, and multicentre results were recorded. Tru-cut or excisional biopsy results of the patients were recorded. In all of these patients whose final pathology result was EPC, sentinel lymph node biopsy (SLNB) was performed so that at least two lymph nodes were excised using the dual method (methylene blue, radioactive agent), and frozen was studied. The type of surgery performed, SLNB results, and whether axillary dissection was performed were recorded. Moreover, the final pathological results of the patients, tumor size, hormone receptor status, adjuvant chemotherapy, radiotherapy, hormone therapy, local recurrence status, and follow-up time were recorded.

**Statistical analysis**
We evaluated the data we obtained statistically. The data evaluation used www.e-picos.com New York software and MedCalc statistical package program. The mean and standard deviation, the minimum and maximum values of the features while making the statistics of the continuous structure, Frequency, and percentage values were used to define categorical variables. A 95% Confidence Interval is given along with the incidence rates.

Results

Sixty-four patients whose final pathology result was EPC screened between January 2012 and January 2022 and whose data were available were included in the study. The mean age of the patients was 64 (27–79). Sixty-two of the patients were female, and two were male. Fifty patients were in the postmenopausal period, 12 were in the premenopausal period, and 12 had a family history of breast cancer. A palpable mass in 36 patients, nipple discharge in 10 patients, symptoms of both a palpable mass and nipple discharge in 11 patients, and seven patients were diagnosed with asymptomatic routine screening results (Table 1).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (Min-Max), years</td>
<td>64 (27–79)</td>
</tr>
<tr>
<td>Median IPC size (Min-Max), mm</td>
<td>27 (8–53)</td>
</tr>
<tr>
<td>Women n(%)</td>
<td>62 (96.8)</td>
</tr>
<tr>
<td>Male n(%)</td>
<td>2 (3.1)</td>
</tr>
<tr>
<td>Family history of breast cancer n(%)</td>
<td>12(18.7)</td>
</tr>
<tr>
<td>Premenopausal n(%)</td>
<td>12(19.3)</td>
</tr>
<tr>
<td>Postmenopausal n(%)</td>
<td>50(80.6)</td>
</tr>
<tr>
<td>Palpable mass n(%)</td>
<td>36(56.2)</td>
</tr>
<tr>
<td>Nipple discharge n(%)</td>
<td>10(15.6)</td>
</tr>
<tr>
<td>Screening n(%)</td>
<td>7(10.9)</td>
</tr>
</tbody>
</table>

The USG report of the patients was reported as BRADS IVa, IVb, IVc (17,29,15 patients, respectively), and BRADS V (4 patients). Except for three patients (2 males, one age 27), the mammography results of the other patients were reported as BRADS IV (59 patients) and BRADS V (3 patients). There was a mass in the right breast in 36 patients and a mass in the left breast in 28 patients. Tru-cut biopsy was performed on 54 patients, including 11 who underwent fine needle biopsy in another center. Excisional biopsy was performed in 7 patients, with wire marking in 3 patients, and biopsy under general anesthesia with the help of ROLL in 2 patients who were not palpable. A definitive diagnosis of EPC could not be made in any
of the patients who underwent FNAB in Tru-cut and an external center. Tru-cut biopsy results of 29 patients had atypical proliferative breast lesions, carcinomatous changes of epidermoid cysts (9), and invasion or DCIS differentiation (15) could not be made clear. Breast surgery was performed in all 54 patients who underwent tru-cut. The final pathologic evaluation revealed that 19 patients (29.6%) had pure EPC, 27 patients (42.1%) had EPC with associated DCIS, and 18 patients (28.1%) had EPC associated with invasion (Table 2).

Table 2
Clinicopathological features and management in patients with EPC.

<table>
<thead>
<tr>
<th></th>
<th>PURE-EPC (n = 19)</th>
<th>DCIS-EPC (n = 27)</th>
<th>INV-EPC (n = 18)</th>
<th>All-EPC (n = 64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLNB (metastas)</td>
<td>0(100%)</td>
<td>0(100%)</td>
<td>1(5.5%)</td>
<td>1(1.5%)</td>
</tr>
<tr>
<td>BCS n(%)</td>
<td>19(100%)</td>
<td>27(100%)</td>
<td>16(88.9%)</td>
<td>62(96.9%)</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>0(100%)</td>
<td>0(100%)</td>
<td>2(11.1%)</td>
<td>2(3.1%)</td>
</tr>
<tr>
<td>ALND</td>
<td>0(100%)</td>
<td>0(100%)</td>
<td>1(5.5%)</td>
<td>1(1.5%)</td>
</tr>
<tr>
<td>ER (+)</td>
<td>19(100%)</td>
<td>27(100%)</td>
<td>15(83.4%)</td>
<td>63(100%)</td>
</tr>
<tr>
<td>(-)</td>
<td>0(100%)</td>
<td>0(100%)</td>
<td>1(5.5%)</td>
<td>1(100%)</td>
</tr>
<tr>
<td>PR (+)</td>
<td>19(100%)</td>
<td>27(100%)</td>
<td>15(83.4%)</td>
<td>63(98.4%)</td>
</tr>
<tr>
<td>(-)</td>
<td>0(0.0%)</td>
<td>0(0.0%)</td>
<td>1(5.5%)</td>
<td>1(1.6%)</td>
</tr>
<tr>
<td>HER-2 (+)</td>
<td>0(0.0%)</td>
<td>0(0.0%)</td>
<td>1(5.5%)</td>
<td>1(1.5%)</td>
</tr>
<tr>
<td>(-)</td>
<td>19(100%)</td>
<td>27(100%)</td>
<td>17(94.5%)</td>
<td>63(98.5%)</td>
</tr>
<tr>
<td>Ki-67 (&gt;20%)</td>
<td>0(0.0%)</td>
<td>1(0.0%)</td>
<td>3(16.7%)</td>
<td>4(6.2%)</td>
</tr>
<tr>
<td>Adjuvant chemotherapy</td>
<td>0(0.0%)</td>
<td>0(0.0%)</td>
<td>1(5.5%)</td>
<td>1(1.5%)</td>
</tr>
<tr>
<td>Radiation therapy</td>
<td>2(10.6%)</td>
<td>5(18.6%)</td>
<td>16(88.9%)</td>
<td>23(36%)</td>
</tr>
<tr>
<td>Endocrine therapy</td>
<td>19(100%)</td>
<td>27(100%)</td>
<td>18(100%)</td>
<td>64(100%)</td>
</tr>
<tr>
<td>Recurrence events</td>
<td>0(0.0%)</td>
<td>0(0.0%)</td>
<td>1(5.5%)</td>
<td>1(1.5%)</td>
</tr>
<tr>
<td>Death</td>
<td>0(0.0%)</td>
<td>0(0.0%)</td>
<td>0(0.0%)</td>
<td>0(0.0%)</td>
</tr>
</tbody>
</table>

All patients (64) underwent SLNB with the dual method to excise at least two lymph nodes. Re-excision was performed for surgical margin negativity in 9 patients with suspected surgical margins or positive surgical margins in the excisional pathology results. Mastectomy was performed on their request in 2 patients whose pathology results were found to be invasive-EPC. As a result of the frozen section performed during SLNB, metastasis was detected in only one lymph node in 2 patients. Axillary lymph node dissection was not performed in any patient in this session. In one of the patients with SLNB
positivity in the final pathology report, metastasis was detected in two sentinel lymph nodes in one of the patients. ALND was performed in the patient. Metastasis was detected in only two lymph nodes as a result of ALND pathology, and it was observed that these two lymph nodes had lymph nodes excised during the sentinel lymph node (Table 2).

Estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER-2) expression, Ki-67 expression was evaluated by immunohistochemistry in all patients. ER/PR was positive in 64 patients and negative in only one patient; this patient was INV-EPC. HER-2 was negative in 63 patients and positive in only one patient. Ki-67 was over 20% in 4 patients; 3 were INV-EPC, and 1 was DCIS-EPC. Patients with hormone receptor positivity received endocrine therapy. Twenty-three patients received radiotherapy, two pure-EPC, 5 DCIS-EPC, and 16 INV-EPC. 1 INV-EPC patient received adjuvant chemotherapy. Local recurrence was detected at 38 months in 1 INV-EPC patient, and this re-excision was performed. The mean follow-up was 64 months, and no patient died.

**Discussion**

In the present study, 64 patients with EPC, one of the rare breast lesions diagnosed with pathology, were analyzed retrospectively; PURE-EPC was detected in 19 patients, DCIS-related EPC in 27 patients, and EPC with invasion in 18. When lymph node metastasis was evaluated, the sentinel lymph node was positive in only one patient with invasion, and no metastasis was observed in the remaining patients.

Encapsulated papillary carcinoma (EPC) is a rare breast tumor that still causes intense debate and uncertainty in diagnosis and treatment due to its frequent association with morphologically different but closely related DCIS and invasive ductal carcinoma. Today, discussions about the categorization and terminology of EPC in the surgical and pathology literature continue. The main reason for these discussions stems from the fact that EPC, unlike classical DCIS pathologically, lacks evidence of myoepithelial cells surrounding neoplastic proliferation. Due to the absence of myoepithelial cells and the rare occurrence of axillary lymph node metastases, EPC, according to the new approach, is accepted as a self-limiting and benign invasive carcinoma with a prognosis similar to carcinoma in situ. To avoid aggressive overtreatment, in the absence of overt invasion beyond the fibrous capsule, the EPC should be evaluated by nuclear grade and staged as pTis (DCIS). In the case of overt invasion, the Nottingham Grading and tumor staging should be based solely on the size and morphological characteristics of the invasive component.

Similarly, ER, PR, Ki67, and HER2 status should be based on the invasive component. However, nowadays, pathologists commonly prefer the term "encapsulated papillary carcinoma" to the more conventional nomenclature "intracystic papillary carcinoma." In our institution, pathologists preferred to use the terms "encapsulated papillary carcinoma" or "encapsulated papillary carcinoma with invasion" instead of IPC after the 2012 World Health Organization Breast Tumors classification. In addition, the presence of DCIS accompanying EPC is reported in pathology reports. This lack of clarity regarding their exact biology and the unpredictability of their association makes establishing guidelines
for management extremely difficult. We named the cases reported as intracystic papillary carcinoma of the 64 cases presented in our study as encapsulated papillary carcinoma in accordance with the new terminology. Of these patients, 19 had PURE-EPC, 27 had DCIS- EPC, and 18 had INV-EPC.

Although EPC can affect patients of all ages, it is generally seen in postmenopausal older women [12]. In our study, most patients were older, and the median age was 64. Although most patients were women, 2 (3.1%) patients were diagnosed in men. This rate is slightly higher than invasive ductal carcinoma and DCIS reported in the male population and is higher than previously described in the literature [13]. It shows that EPC is not a female-specific entity, and breast cysts in males may occasionally contain a malignant component [13]. The most common complaint in all patients at presentation is palpable mass, less frequent nipple discharge, and incidentally detected cases during general breast screening, which are similar to other publications in the literature [3]. The median tumor size of all EPC in our study population was 27 mm, similar to other publications in the literature [12, 14].

In EPC, the mass is often retro areolar and well-circumscribed. In ultrasonography, irregular borders or lobulations, solid components within the cystic structure, intra-cyst septations, and papillary structures into the lumen can be observed. In addition to the mass, a microcalcification cluster can also be found in mammography. Breast cysts, especially in postmenopausal women, should be regarded with suspicion, and the solid structures within the cyst should be carefully evaluated. There may be at least one abnormal feature in our series of radiological imaging data obtained from mammography and ultrasonography. In cases where core biopsy does not diagnose invasion, chest wall invasions such as micro and macro calcifications, micro and macro lobulations, irregular, blurred, and thickened borders, and cystic septations and pectoralis muscles can be seen. Speer et al. reported that their studies did not define the radiological features to distinguish between non-invasive and invasive intracystic papillary carcinoma [15]. In our study, radiological imaging was generally reported similarly.

Papillary neoplasms can be recognized by needle aspiration or tru-cut biopsy, but an excisional biopsy is often needed for diagnosis. In a study evaluating 45 patients with intracystic papillary carcinoma, the diagnosis of papillary cancer was definitively established in only 43% of cases with tru-cut biopsy, and excisional biopsy was required for diagnosis in other patients [15, 16]. Solorzano et al. evaluated 40 patients with intracystic papillary carcinoma and found that needle aspiration biopsy failed to diagnose in 41% of cases; they reported that tru-cut biopsy could not detect invasion in 30% [14]. In intracystic papillary cancers, invasion is usually found at the periphery of the lesion, tru-cut biopsy is done from the middle of the mass, and this may be the reason for false negatives. It may also be difficult to distinguish the diagnosis of EPC from benign papillary lesions. It is estimated that papillary breast lesions are present in up to 5% of breast biopsy specimens and include papilloma, papillomatosis, sclerosing papilloma, atypical papilloma, papilloma with atypical ductal hyperplasia, intraductal papillary carcinoma and invasive papillary carcinoma [16, 17]. In our study, the patients could not be diagnosed with FNAB, and most of these fine needle patients were applied to our polyclinic from an external center. In our practice, we do not routinely use fine needle aspiration for diagnosis. Fine-needle aspiration biopsy results in our study consist of patients who applied to our clinic with the results of an external center and
were followed up in our clinic. We cannot diagnose EPC with a Tru-cut biopsy, and the definitive result is
diagnosed with an excisional biopsy. We prefer to perform an excisional biopsy with wire marking and
roller in nonpalpable patients. The diagnostic difficulty arises from both tumor heterogeneity and the
biological behavior of EPC. Therefore, surgical resection is a necessary step for accurate pathological
diagnosis. Therefore, an excisional biopsy can be started in these patients for diagnostic and therapeutic
purposes.

In light of historical data, the priority in the surgical treatment of EPC is breast-conserving surgery with a
negative surgical margin [14, 16, 18]. In our series, we performed breast-conserving surgery in 62 patients
and total mastectomy in only two patients. Two patients who underwent mastectomy were retro areolar
localized, and the pathological results were invasion-related EPC. We applied this treatment at the request
of the patients. Our basic surgical margin behavior is to target the tumor at 1 cm macroscopically and 1
mm microscopically during surgery. However, we are moving towards a more minimally invasive surgical
margin, and since it is not very aggressive in this tumor, it can be considered adequate for no-ink surgery.
Therefore, we did not perform surgical excision in cases without ink. In DCIS, the surgical margin should
be 2 mm, but when there is an invasive component, no-ink is sufficient for these as we determine the
surgical margin according to invasion.

In previous studies, ALND has been recommended only in cases of invasive carcinoma-associated or,
rarely, carcinoma in situ [17]. Today, axillary dissection has begun to be questioned for these tumors, and
it has been reported that sentinel lymph node biopsy will be sufficient to evaluate the axilla [6, 12, 19]. In
our study, we performed SLNB with the dual method to evaluate the axilla in the same session in all the
cases we operated on, and as a result, we applied ALND to 1 patient, and this patient was a patient with
INV-EPC. In addition, the pathology result of this patient was not reported as metastasis. None of the
PURE-EPC and DCIS-EPC patients were found to be SLNB positive, and ALND was not performed.
However, the primary debate is whether SLNB should be applied to each case to evaluate the axilla in EPC
cases. In a publication with two case reports in the literature, the presence of lymph nodes containing
micro invasion in the axilla was found in two case reports with pure EPC. Therefore SLNB was
recommended for every EPC case [20]. However, most publications recommend SLNB only in cases with
accompanying invasion [6, 10, 12, 14]. It seems appropriate to perform SLNB in cases associated with
invasion or DCIS. However, in our study, the negative SLNB results in patients with EPC and the fact that
only one patient with INV-EPC was positive and considering that this was reactive as a result of axillary
dissection suggests that we perform SLNB unnecessarily in EPCs. Although SLNB is a minimally invasive
procedure, it has known side effects, and we recommend performing an SLNB in these cases, which are
primarily seen in the elderly and have a good prognosis, according to the final pathology result. We can
protect the patient from complications that may occur during SLNB.

These tumors are frequently low nuclear grade, without necrosis, hormone receptor-positive, and curb-B2
negative [17, 20]. These data are similar to our cases. Only 1 of our patients was reported triple negative,
and all of these patients were associated with invasion.
Today, radiotherapy (RT), hormone therapy, and chemotherapy are performed in these cancers, but it is still being determined how it will be applied to which patient. Solorzano et al. applied RT to 30% of intracystic papillary carcinoma cases and emphasized whether radiotherapy affected recurrence and survival. In other studies, it has been reported that RT and hormone therapy can be applied, especially in cases of high nuclear-grade intracystic papillary carcinoma younger than 50 years of age, and this decision should be made on a case-by-case basis [6, 12, 14, 16].

Fayanju et al. published that patients with EPC and DCIS or micro invasion are more likely to be treated with adjuvant radiotherapy than patients with pure EPC (16). In another study, 50% of patients received hormonal therapy, and 43.8% received radiation therapy for invasive tumor-associated EPC. The mean follow-up period of the patients was 63 months, and only one patient developed local recurrence, and no mortality was observed during the follow-up period. The patient with recurrence was in the invasive EPC group. This is similar to other reports showing excellent prognosis and low recurrence rates in EPC patients. Solórzano et al. reported 13 patients (32.5%) who relapsed after a median follow-up of 58 months [14]. Leal et al. He had a median follow-up of 42 months and reported one local recurrence in a patient treated with lumpectomy alone [21, 22].

Our current study has limitations such as being retrospective, various percutaneous biopsy techniques used, and the fact that the cases were not drawn from randomized patient series. In addition, the fact that it is a single-center study is among other limitations. Despite these limitations, our study will significantly contribute to the literature regarding the number of cases and the long follow-up period.

**Conclusions**

SLNB applied in the staging evaluation of patients with EPC does not affect treatment outcomes and survival. Therefore, surgical excision with a negative margin may be performed without SLNB alone in the first-line diagnosis and treatment of EPC patients. In addition, patients can be followed up without adjuvant radiotherapy and chemotherapy. Adjuvant radiation and endocrine treatments may be considered in patients with EPC, especially in younger patients. This study may help guide the diagnosis and treatment of breast EPC.

**Declarations**

**Statement of Ethics**

This study protocol was reviewed and approved by The Board of Ethics Committee of Mersin University on 25/04/2022 with approval 2022/294. Written informed consent was obtained from all patients for this study.

**Conflict of Interest Statement**

The authors have no conflicts of interest to declare.
Funding Sources

The study received no funding.

Data Availability Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Author Contributions

All authors materially participated in this research, were involved in the preparation of this article, and approved the final version. Cumhur Ozcan, Ahmet Dag and Ferah Tuncel were involved in the study conception and design. Sami Benli were involved in acquisition, analysis and interpretation of the data. Cumhur Ozcan, Ferah Tuncel wrote the initial draft of this paper. Ahmet Dag, Sami Benli, were involved in the critical revision of this work.

References


