Encapsulated Papillary Carcinoma of the Breast: An Invasive Tumor With Excellent Prognosis

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Abstract: Papillary carcinoma (PC) of the breast, which accounts for 0.5% to 1% of breast cancer, is a distinct histologic subtype that is characterized by malignant epithelial proliferation supported by fibrovascular stalks. However, the classification of PC (whether they are in situ or invasive), its behavior, and management remain a matter of debate.

Methods: In this study, we reviewed 302 PCs including 247 pure PCs without coexisting conventional non-PCs collected from 3 institutions. This included 208 (84%) intracystic PCs (IPC), 30 (12%) solid PCs (SPC), and 9 (4%) papillary ductal carcinoma in situ (DCISs). In addition, previous studies of PC were reviewed. This included 339 pure PCs of a total of 521 PC patients. Clinical and outcome analyses were carried out to assess nature and behavior of these lesions and to determine their optimal outcome-based management.

Results and Conclusions: SPC is more frequently associated with coexisting conventional invasive carcinoma than IPC ($P < 0.05$). Although the majority of papillary DCIS and some cases of IPC and SPC (both called encapsulated PC) that are surrounded by an intact layer of myoepithelial cells are considered to be true in situ lesions, PC lacking a peripheral layer of myoepithelial cells can be regarded as a special type of invasive carcinoma associated with low incidence of stromal/skeletal muscle invasion, low frequency of lymph node metastasis (3%), and infrequent development of local or distant recurrence. These lesions are therefore characterized by indolent behavior and extremely favorable prognosis. Encapsulated PC can be treated with adequate local therapy. Routine use of adjuvant therapy, particularly chemotherapy, is clearly not appropriate in view of the very low risk of subsequent events. However, hormonal therapy may be indicated in certain cases such as recurrent PC.

Key Words: human breast carcinoma, papillary carcinomas, encapsulated, intracystic, solid, prognosis and outcome

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Papillary carcinoma (PC) of the breast, which accounts for 0.5% to 1% of breast cancer, is a distinct histologic subtype that is characterized by malignant epithelial proliferation supported by fibrovascular stalks.[2,9,15,23,26,27,37,48,51] PC can be either localized, forming an expansile mass corresponding to intracystic/encysted (IPC) and solid (SPC) variants of PC, or it can diffuse within terminal duct lobular units and correspond to papillary variant of ductal carcinoma in situ (papillary DCIS).[1,6,9,37,44,51] Compared with IPC, SPC is typically solid, characterized by mucin production and neuroendocrine features, and is more often multinodular,[44,54] whereas papillary DCIS is typically surrounded by a peripheral layer of myoepithelial cells.[1,9] The term encapsulated PC (EPC) has recently been introduced to define IPC[4,8,20] and SPC[44,54] that are typically circumscribed and often encapsulated (separated from the surrounding mammary stroma by a fibrous capsule) and lack myoepithelial cells at their periphery. In this study, we use the term EPC to include both IPC and SPC.

PC can be present as an isolated lesion or associated with conventional nonpapillary in situ or invasive carcinoma. However, the term PC is used in the literature to describe a heterogeneous group of malignant neoplasms including noninvasive (in situ) and invasive carcinomas, and its classification remains extremely varied. The discrepancies between classifications have important implications for patient management.[1,23,37,49–51]

IPC and SPC have long been regarded as a form of in situ carcinoma, but the observation of the absence of myoepithelial cells at the tumor-stromal interface[8,20,24,28,35,55] has led to the proposal that these lesions are, in fact, invasive carcinomas with an expansile growth pattern.[8,20,23] The adoption of this concept is supported by the results of some studies, which reported cases with axillary nodal[32,35] or distant metastases (DMs)[15,25,48] developing in patients after a diagnosis of PC lacking conventional morphologic forms of invasion.

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What constitutes invasion in EPC is not well defined, and different authorities use different definitions; the majority of these are not based on clinical behavior. The World Health Organization's definition of invasive PC, for instance, states that "when PC invade, they generally assume the pattern of ductal carcinoma and lack papillary architecture,"[1] a view that is shared by many other authorities.[13,37,44,51] Despite the widely accepted understanding of invasion as an unequivocal invasion of nonspecialized stroma by conventional non-papillary-type carcinoma, the definition of invasion in PC remains confusing. For example, in the World Health Organization classification "invasive PCs are characteristically circumscribed, show delicate or blunt papillae, and show focal solid areas of tumor growth."[1] Consistent with the latter definition, some authorities reserve the term invasive PC for infiltrating carcinomas exhibiting an exclusively papillary morphology.[37] In an attempt to differentiate in situ from invasive PC, some researchers defined invasion as nests showing papillary architecture displaying a pattern inconsistent with that of branching ducts or terminal duct lobular units. These nests should be located within nonspecialized stroma (blunt invasion).[23,35,37] However, others define stromal invasion by the presence of clusters of PC 10 mm or more beyond the capsule.[25] However, the latter researchers did not ascribe any clinical value to this form of stromal invasion,[25] and this definition has also been criticized by others.[24] Even researchers who believe that EPCs are best considered as in situ carcinomas based on the finding of a well-defined layer of basement membrane material at the periphery[14] and their clinically indolent behavior,[6,14,19,37,51] accept that a subset of these tumors may represent low-grade invasive carcinomas exhibiting an expansile type of infiltration.[16,37,51] Identification of this subset, however, remains ill defined and problematic.

As a consequence of these observations and the difficulty in distinguishing in situ from invasive EPC, a proportion of these cases will potentially be called invasive PC. Subsequently, for the purposes of clinical management, pure PC may be grouped with cases of PC associated with the more aggressive conventional-type invasive carcinomas. However, it may not benefit from adjuvant treatment. This concern is supported by the varied proportion of cases termed as invasive PC (from 13%[15,19] to 59%[34] of PC in these series were invasive). Interpreting the literature on PC is challenging, as a large proportion of studies are individual case reports and large series often include an amalgam of morphologic types.[18,26,27] In addition, although the management of PC associated with conventional invasive carcinomas has generally been administered according to the standard of care for the more aggressive non-PC component, therapeutic management of pure PC is less clear. Therefore, in this study, we performed a retrospective analysis of a large series of pure PC (without coexisting conventional invasive carcinomas) with a long-term follow-up comprising clinicopathologic and outcome information. In addition, previous studies concerning pure PCs were reviewed, and clinical and outcome data were analyzed. Our aims were (1) to determine whether these lesions are in situ or invasive tumors, (2) to assess clinical features, behavior, and outcome of PC, (3) to identify features associated with invasive/aggressive clinical behavior, and (4) to compare IPC and SPC.

METHODS

A retrospective search of the pathology database at the Nottingham University Hospital NHS Trust (NUH) was carried out. Cases diagnosed during the period 1990 to 2010 as IPC, SPC, papillary DCIS, invasive PC, or PC not otherwise specified were retrieved.

This resulted in 204 cases; however, after initial revision, 29 cases were excluded because of (i) incorrect coding (4 cases), (ii) repeat biopsy from the same patients (3 cases), or (iii) the presence of synchronous invasive carcinoma of different histologic type (no special type, micropapillary, or mucinous: 22 cases). The remaining 175 cases were included in the analysis, and these comprised 55 patients diagnosed and treated at NUH and 120 cases who were referred to NUH for an expert opinion and were treated in other centers. This study included additional series of PC patients diagnosed and treated between 2000 to 2010 who were retrieved using the same search criteria from the databases of pathology departments of (1) Leicester University Hospitals NHS Trust, Leicester, UK (68 PC patients) and (2) Hospital de Bellvitge, Barcelona, Spain (30 PC patients). Of these 98 PC patients, 26 cases were excluded due to the presence of coexisting conventional nonpapillary invasive carcinomas, leaving 72 cases that were included in the final analysis.

The patient's clinical history and tumor characteristics including patients' sex, age at presentation, surgical procedure, primary tumor size, associated nonpapillary DCIS and its nuclear grade, and lymph node (LN) status (total number and number of positive nodes) were obtained from the database. In addition, case files of nonconsultation cases were subject to detailed review to assess survival data including survival time, disease-free survival, and development of DM, local, regional contralateral recurrence. Disease-free survival was calculated from the date of first operation, with first recurrence, local, regional, or distant, being scored as an event, and with censoring of other patients at the time of the last follow-up or death. Local recurrence was defined as tumor arising in the treated breast or chest wall. Regional recurrence was defined as tumor arising in the axillary or internal mammary LNs.

Cases were subjected to histologic review to identify and relate histologic features to clinical behavior, and these include histologic subtype[1,6,9,37,44,51] and histologic grade,[1,41,44] presence of stromal or vascular invasion (VI), presence of myoepithelial cells, and histologic type of recurrent/metastatic tumor foci whenever present. Microinvasion or pseudoinvasion was defined as areas suspicious

of invasion by papillary, cribriform, and/or solid clusters of tumor cells in the surrounding stromal tissue, which are not enough for a designation as conventional-type invasive carcinomas. These could represent an entrapped malignant epithelium in the surrounding sclerotic/fibrotic areas or resulting from previous biopsy procedure. The latter group was included to assess whether the presence of suspicious areas of invasion in PC influences clinical behavior. This study did not include papilloma with atypia or micropapillary DCIS without papillary components.

A range of diagnostic biomarkers was also available on a subset of these tumors, including myoepithelial markers (smooth muscle actin, smooth muscle myosin heavy chain, cytokeratin 5/6 (CK5/6), CK14, and p63), CK7, CK18, HER2, and estrogen receptor.

In addition, the literature, including PubMed, Medline, and the Cochrane library, was searched for articles from 1980 to 2010 published in English. The keywords used for the search were "breast cancer," "papillary," "intracystic," "encysted," "solid," and "outcome." Publications before 1980 or that were published in other languages were also considered if they were commonly referenced or were highly regarded. The search also included the reference list for these articles and selected additional articles and web pages that were judged to be relevant.

RESULTS

A total of 302 cases of PC were identified from the 3 institutions included in this study. Of these, 247 cases were identified as pure PCs. Tumors diagnosed as pure EPC (pure IPC and pure SPC), papillary DCIS, and PC associated with DCIS and/or microinvasion or pseudoinvasion were included. Of all cases, 208 (84%) were diagnosed as IPC, 30 (12%) as SPC, and 9 (4%) cases were diagnosed as papillary DCIS (Table 1). Forty-three cases (17%) were diagnosed as PC associated with possible invasion, microinvasion, or extravasation of mucin. The architecture of PC is papillary, but often shows cribriform and/or solid areas with low-to-intermediate nuclear grade (45% were grade 1, 51% grade 2, and 4% were grade 3). Data on associated DCIS were available on 181 cases; of these, 128 (71%) cases were associated with DCIS in the surrounding tissue (43% were low grade, 42% intermediate grade, and 15% were high grade). All cases with available immunohistochemistry results showed a estrogen receptor-positive HER2-negative phenotype and diffuse strong expression of luminal CKs (30 cases). Staining of myoepithelial markers was absent apart from occasional cells positive for basal CKs and/or p63 at the periphery of cystic PC lesions (45 cases), but they were detected around papillary DCIS in 8 cases (89%).

Clinicopathologic Features

The median age of patients with pure PC was 69 years (range, 30 to 93 y). The majority of PC cases were diagnosed in women (98%). The median size of the lesions was 17 mm (range, 2.5 to 100 mm). The type of surgery was available in 122 cases; of these, 22% were treated with mastectomy. VI was identified in 5 cases (Table 1 and Fig. 1). LN positivity was found in 4 cases (6% of cases with LN surgery performed).

TABLE 1. Clinicopathologic Features of IPCs and SPCs*

Variables	IPC Number = 207	SPC Number = 30	*P*
Age: Median (range) years	69 (30-85)	76 (48-89)	0.022
Size: Median (range) mm	17.5 (3-90)	15 (3-32)	0.101
Grade			
1	63 (47%)	12 (40%)	0.118
2	67 (50%)	15 (50%)	
3	3 (3%)	3 (10%)	
Associated DCIS			
No	43 (30%)	9 (33%)	0.820
Yes	102 (70%)	18 (67%)	
VI			
Negative	165 (98%)	19 (95%)	0.432
Positive	4 (2%)†	1 (5%)‡	
LN status§			
Negative	61 (97%)	15 (88%)	0.023
Positive	2 (3%)	2 (12%)	
Recurrence			
No recurrence	78 (86%)	24 (96%)	0.305
Diagnosed as recurrent‖	6 (6%)	1 (4%)	
Recurred during follow-up	7 (8%)	0 (0%)	

*Nine cases of papillary DCIS were not included in this table.

†Two cases were recurrent carcinomas following previous papillary and ductal/no specific type carcinomas, whereas 2 cases showed no evidence of previous or coexisting invasive carcinomas or evidence of LN metastasis or recurrence during a period of 1-year and 5-year follow-up, respectively.

‡This case was SPC with mucin lakes suspicious of invasive mucinous carcinoma and this case showed LN micrometastasis but no recurrence during 2-year follow-up.

§LN staging surgery was performed in 70 cases with a median number of 4 nodes per case (range, 1 to 18). On review, 2 IPC cases, which showed LN micrometastasis with papillary architecture were recurrent carcinomas. The other 2 cases were SPC; both showed focal mucin lakes suspicious of invasive mucinous carcinoma (1of 2 and 1 of 1 nodes positive).

‖Cases diagnosis in this study as PC following previous malignancy in situ or invasive in the ipsilateral or contralateral breast.

In this study, 8 PCs showed stromal/fat invasion (7 IPC and 1 papillary DCIS) and 5 showed skeletal muscle invasion (4 in the pectoral muscle and 1 in the proximal part of the rectus abdominis) (Fig. 2). Seven of these 8 cases were recurrent tumors diagnosed 1 to 7 years after the initial diagnosis of malignancy. Five cases followed previous mastectomies for DCIS or IPC, and 1 case followed local excision of IPC. We believe that it is notable that the extent of local infiltration was related to the frequency of recurrences. The 2 cases with extensive stromal and skeletal muscle invasion had a history of 6 and 11 surgical interventions. In the latter, there was infiltration of muscle in the presternal and epigastric regions. The last case was a contralateral recurrence. Interestingly, all these invasive foci maintained their cystic papillary morphology with absence of surrounding myoepithelial cells, and some of the intramuscular foci were surrounded by fibrous capsule with basement membrane-like (collagen type 4 and laminin positive) material similar to that seen around localized EPC. immunohistochemistry studies of the previous primary

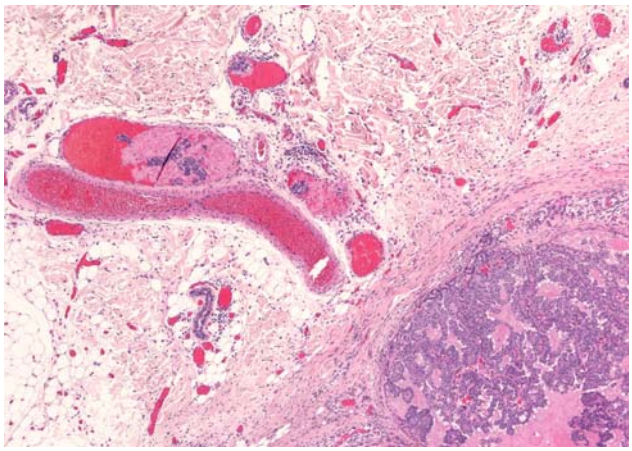

FIGURE 1. A case of EPC showing VI. This case was a recurrent PC that showed VI as demonstrated by the presence of malignant cells admixed with fibrinous material within the lumen of multiple vascular spaces. No evidence of previous core biopsy site reaction or microinvasion outside the fibrous capsule could be identified close to the involved vascular space.

tumors were available in 6 cases and showed absence of myoepithelial cells around IPC and DCIS-like areas with papillary and cribriform-like patterns.

No muscle invasion was seen in other cases. The remaining cases, which were reported as invasive PC or PC with suspicion of invasion, were diagnosed mainly based one or more of the following: (1) absence of myoepithelial cells around papillary/cribriform-like areas, (2) absence/attenuated capsule around papillary clusters, or (3) microinvasion just beyond specialized stroma with a possibility of invasion/core biopsy site.

Outcome Analysis

Follow-up data were available in 108 cases (excluding patients diagnosed with papillary DCIS or diagnosed solely by core biopsy or cases with a history of previous nonpapillary mammary carcinoma), with a median of 53 months (range, 4 to 178 mo). During that period, 7 cases developed local recurrences. Five had characteristics of metachronous second primary breast cancers; 1 recurred after 84 months in the same breast as extensive DCIS and a focus of invasive grade 2 ductal no specific type (NST) carcinoma together with multiple foci of IPC. The other 4 cases recurred as pure nonpapillary DCIS after 9, 13, 42, and 86 months, respectively. One case recurred as a nodule of IPC 6 months after mastectomy for IPC with DCIS. The last case was reported as grade 3 IPC associated with high-grade DCIS but with negative LN (0 of 3). However, slides of the recurrence were not available for review. The first recurrence was 20 months later in the axilla with positive LN (2 of 13 LN positive). Fifty months later, the patient had mastectomy, which showed 14 foci of PC, ductal (NST), and mucinous carcinomas. This patient developed liver metastasis and died of breast cancer 32 months later. However, no histology of the metastasis was available. During the period of follow-up, 15 patients died of unrelated causes.

Of note, there were 11 PC cases diagnosed solely on needle core biopsy, and these cases were not included in the main study group. These 11 cases comprised 6 consultation cases with no data on further surgery and 5 elderly patients (range, 73 to 85 y) treated with hormone therapy alone after needle core biopsy diagnosis. Importantly, none of the 5 elderly patients showed disease progression during the follow-up period [median, 48 mo (range, 39 to 77 mo)].

DISCUSSION

Malignant papillary lesions of the breast include (1) benign papilloma involved by DCIS, with or without DCIS in the surrounding parenchyma. This entity usually presents as solitary lesions central in location and

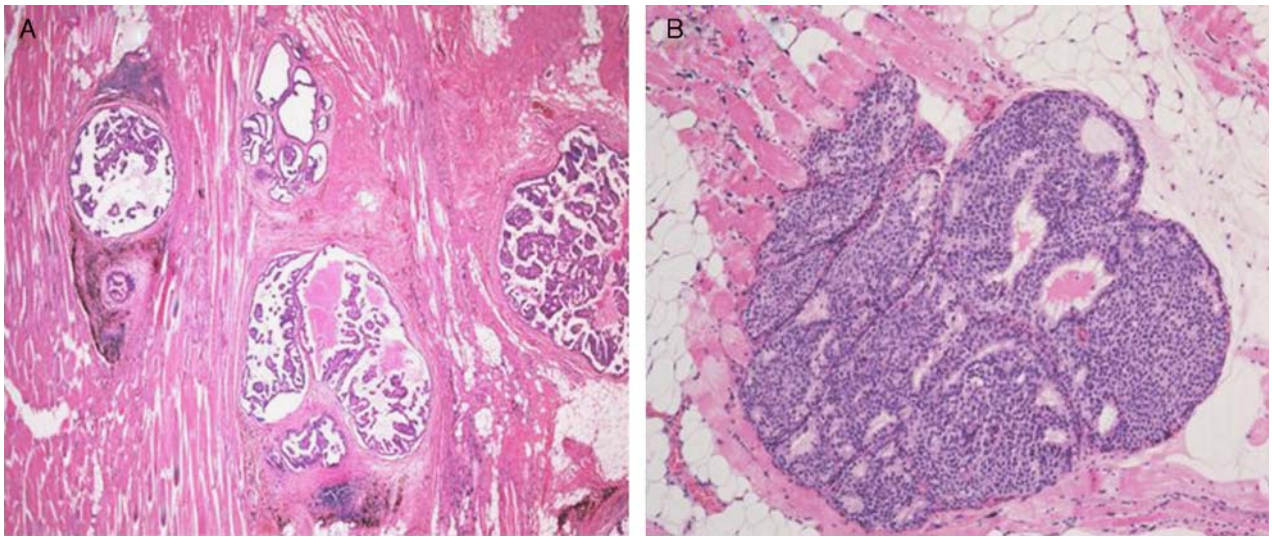

FIGURE 2. EPC showing skeletal muscle invasion with (A) or without (B) the peripheral fibrous capsule. full color online

it is recognized as an in situ process that maintains myoepithelial cells at the tumor/stromal interface and within the lesion.[9,37,44,51] (2) the papillary variant of DCIS, which has a myoepithelial layer at their periphery.[20,50] It may be mixed with other subtypes of DCIS and presents as a diffuse lesion in a mammary duct system. (3) EPC, which includes both IPC and SPCs, usually presents as unilateral palpable masses (70% to 90%) or nipple discharge (5% to 25%) in elderly women. The intraductal nature of the first 2 types of PC is well-recognized and they are managed such as other forms of DCIS. However, the nature of EPC is controversial; whether they are in situ or invasive, their behavior and their optimal clinical management. In addition, the comparative behavior of IPC and SPC is uncertain.

This study includes the largest series of PC with histologic review and follow-up data in addition to review data on PC series included in previous studies (Table 2). Our results are consistent with previous studies, which reported that the median age of women with EPC varied from 63 to 75 years (average, 70 y for IPC[2,6,19,24,25,31,48,50,55] and 73 y for SPC[28,34]). The management of these lesions varies considerably, with mastectomy rates varying from 7%[19] to 88%[50] (average, 58%[6,14,15,19,24,25,28,48,55]). This relatively high percentage of mastectomy may be a reflection of more historical series, high rate of failed breast conservation secondary to positive margins (15% to 30%[5,15,25]), or patient preference. In this study, 22% of informative cases underwent mastectomy.

The median size of PC in this study was 18 mm consistent with the literature (12 mm to 35 mm, with an average of 20 mm).[31] Consistent with our results, the majority of PCs are low-to-intermediate grade with 0%[14,34] to 14%[22,43,47,57] being high grade.

Observations of IPC

Previous series of PC included 269 IPCs without invasion and with or without DCIS (Table 2). LN positivity was detected in 3 of 111 cases from series with full details (3%). In addition, LN positivity was reported in 3 IPC cases in 2 different case report studies.[14,15,25,48,55] In the 6 cases with LN positivity, metastasis was in the form of micrometastatic deposits involving only 1 or 2 nodes.

Local breast/chest wall recurrences were reported in 18 cases; 4 as pure IPC, 7 as infiltrating PC, 5 as invasive non-PCs, and 2 cases in which recurrence was not characterized. In addition, 1 case recurred as pure IPC in the axilla. Therefore, the total local/regional recurrence rate was 7% of all 269 cases. Six of 266 patients with IPC without coexisting invasion developed DMs [4 bone and 2 lung metastasis; 4 to 7 y after initial diagnosis (median, 7 y)].[14] However, in 1 case, DM developed after intervening local recurrence as invasive ductal NST carcinoma and the metastasis was histologically different from PC.[15] In the remaining 5 cases, the papillary nature of the metastatic lesion was confirmed histologically only in 1 patient.[15,25] Primary IPC was associated with DCIS in 3 cases,[25] with stromal invasion in 1 case,[55] and in 1 case PC showed in-breast recurrence as IPC before development of DM.[15] None of these cases had positive LN at initial presentation or received hormonal therapy for their primary tumor, except for 1 patient who developed lung metastasis after receiving hormonal therapy for IPC with DCIS. This was the only patient with IPC reported to die of breast cancer.[18]

Consistent with the previous results, 2 cases of IPC in this study showed LN micrometastasis (1%). Both were recurrent carcinomas with stromal invasion, and 1 showed VI. Local invasion/chest wall recurrences were found in 13 cases (14% of informative cases): 6 cases were diagnosed as IPC after previous DCIS or PC and all those cases showed stromal/fat invasion (of 7 cases in total), and 4 of them showed skeletal muscle invasion.[35] Seven cases developed recurrence during the follow-up period. The only case with DM and breast cancer-related death in this study developed intervening recurrence as nodal metastasis and then as invasive ductal/NST breast carcinoma.

Observations of SPC

Previous studies of SPC included 67 pure SPCs with or without extravasation of mucin or microinvasion (Table 2). Of these, LN sampling was performed in 43 patients. One case of SPC with microinvasion showed micrometastatic deposits in 2 nodes.[34] In addition, it was reported that in another case of SPC with invasion, LN metastasis showed morphology indistinguishable from SPC in the primary tumor.[35,50] Follow-up data were available in 52 patients; of these, 2 patients developed local recurrences (after 3 and 5 y)[35]; 1 was invasive lobular carcinoma.[34] Distant metastasis was reported in 1 case of SPC with extravasation of mucin and signet-ring cell morphology and with negative LN, who developed metastatic signet-ring cell tumor after 10 years, and it was presumed to be breast primary.[28] This patient was the only patient who was reported to die after a diagnosis of pure SPC. However, in another patient with SPC associated with invasion who developed lung metastasis, the metastatic deposit was histologically indistinguishable from primary SPC.[15,19]

Consistent with these results, 2 cases of SPC in this study showed LN micrometastasis (7%), and both were primary SPCs associated with mucin lakes suspicious of coexisting invasive mucinous carcinoma (of 3 cases in total). Stromal invasion was seen in another 2 cases, but with no evidence of LN metastasis or recurrences. Local recurrences were found in 1 case, which was a new primary (pure DCIS) after 13 months. No DM or breast cancer-related death after SPC was found in this study.

Predictors of Aggressive Behavior

Previous studies have reported a coexisting invasive conventional-type carcinoma in 13%[48] to 32% of IPCs,[14,15,19,24,25,48,55,56] with an average of 27% (93 of 338).[35] The association between SPC and coexisting invasive carcinoma varied from 45%[28] to 80%,[28,34–36,50] with an average of 63% (90 of 143).[25] This difference is

TABLE 2. Previous Studies of PCs Including Intracystic (IPC) and Solid (SPC) Variants

Study (Time Period)	PC Subtype	LN Status	Local Recurrences	DM	Breast Cancer-Related Death	Comments
IPC						
Carter[5] (1949-67)	14 PC	0/14	None	None	None at 5-year and 10-year follow-up	7 patients died of unrelated causes
Carter et al[6] (1949-70)	41 IPC	None (0/11)	3 cases; following local excision and all had associated DCIS; 2 invasive and 1 PC	None (0/41)	None after 5-year (29 patients who had mastectomy) to 10-year (11 patients) follow-up	
Lefkowitz et al[25] (1970-79)	A–49 IPC alone B–28 IPC with DCIS	A–1 patient had 2 positive axillary nodes at presentation and died of unrelated cause after 66 mo with no evidence of recurrence. B–None	6 patients (1 showed stromal invasion at presentation) had local recurrence in the chest wall; 5 presenting as infiltrating PC and 1 as ductal NST. Of the recurrent tumors, 2 showed stromal invasion; 1 also showed associated DCIS. 50% showed grade 3 nuclei	A–None (0/35) B–2 patients developed DMs (lung bone and brain); 1 was alive with tumor at 193 mo and 1 alive with tumor at 60 mo. Histology of metastasis was not known*	0 (28 died of unrelated causes)	Mean follow-up was 11.3 y (6-251 mo). 10-year disease free survival rate was 91% and breast cancer specific survival is 100%. When IPC recurred or metastasized, it did so as invasive PC in 6 of 7 cases
Leal et al[24] (1978-95)	A–9 IPC alone B–9 PC with DCIS C–11 PC with invasion	A–None (0/5) B–None (0/7) C–1 (1/7)	One patient with IPC alone developed a local recurrence after 5 y. Recurrence was similar to primary tumor without associated DCIS or invasion	Not reported	One patient with IPC with invasion died of suspected DM but no histologic confirmation was available	Median follow-up was 42 mo (1-240 mo) 5 patients died; in 4 the cause was unrelated
Harris et al[19] (1979-97)	A–15 IPC B–5 PC with invasion C–3 PC with invasion	A–None (0/7) B–None (0/5) C–Not given	A–1 (IPC alone with negative nodes) after 16 mo and remained disease free after 12 y of follow-up B–No follow-up C–Not given	A–None B–No follow-up given C–Not given	A–None B–No follow-up given C–No follow-up given	
Solorzano et al[48] (1985-2001)	A–14 IPC, B–13 had PC with DCIS, C–13 had PC with invasion	A–None B–None C–3 In total 3/28 positive nodes	A–1 (1/14 recurred as pure IPC) B–2 [2/13 recurred; 1 as PC in the axillary (2 cm after 28 mo and died of other cause 9 y later) and 1 as local DCIS/new primary after 3 y] C–1 (1/13)	A–None B–1 (1/13 developed bone metastasis after 7 y) C–None (0%)	A–0 (3 died of unrelated causes) B–0 (4 died of other causes and 1 alive with disease) C–0 (4 died of other causes) breast cancer specific survival was 100%	Median follow-up time was 58 mo (range, 5-192 mo). The patient who had PC and DCIS who developed DM was alive at end of follow-up. 2 patients who developed recurrence has LN sampled and they were negative.
Hill and Yeh[20] (1994-2003)	A–9 IPC B–4 invasive PC	None	None (0/11)	None (0/11)	None (0/11)	Mean follow-up, 48 mo (range, 5-97 mo)
Fayanju et al[15] (1995-2006)	A–21 IPC B–18 IPC with DCIS C–6 IPC with microinvasion with or without DCIS	A–None (0/6) B–not given C–not given	A–1 patient after 34 mo. She is alive without evidence of disease. B–None C–None	A–0 B–1 (IPC developed pulmonary metastasis and died of the disease. The lung metastasis histology was consistent with breast papillary primary lesion. C–None	At study follow-up, 42 patients were alive without evidence of disease apart from 1 patient died of lung metastasis	Patient who developed D metastasis had received adjuvant radiation and endocrine therapy for primary lesion

TABLE 2. (*continued*)

Study (Time Period)	PC Subtype	LN Status	Local Recurrences	DM	Breast Cancer-Related Death	Comments
Mulligan and O'Malley[32]	A case report of 2 patients with IPC and nodal metastasis	In both cases LN showed micrometastatic deposits	Not reported	Not reported	Not reported	Not reported
Gore et al[17]	A case report of IPC with microinvasion	One node (1/12) showed micrometastasis with papillary architecture	Not reported	Not reported	Not reported	Not reported
Grabowski et al[18] (1988-2005)	A–IPC noninvasive (427) B–Invasive PC (490)	Not given	A–Not given B–39 invasive PC (7.8%) were classified as regional disease, with either direct extension into adjacent tissue or axillary LN involvement. Details not given	A–Not given B–2 cases of invasive PC were reported as metastatic at the time of diagnosis	The relative survival of all patients with IPC, both CIS and invasive, was 97.3% after 5 y and 95.6% after 10 y	Population-based study with no histologic review
Seal et al[46] (1995-2009)	5 Pure IPC with apocrine features	None (0/3)	None	None	None	Median follow-up time 17 mo (3-41 mo)
Esposito et al[14] (not given)	A–21 IPC alone B–6 PC with invasion	A–1 (1/11 micrometastasis in 1 of 4 nodes but there was no histologic review of the LN metastasis) B–1 (1/5 metastasis in 2 nodes which was similar to invasive component)	A–1 [ipsilateral breast (local) recurrence as an invasive ductal NST, 7 y later] B–1 (1/4; regional node recurrence after 3 y followed by bone and lung metastasis 2 y and 4 y later. This tumor showed nonpapillary morphology)	A–1 (same patient who developed local recurrence as NST presented with bone metastasis that was histologically different from PC) B–2 (2/4)	Not reported	Median follow-up 40 mo (8-108 mo) In the IPC with LN positive, primary tumor was not submitted in total and LN slide was not available for review to comment of the subtype of invasion
Wynveen et al[55]	A–IPC with (8 cases) or without (13 cases) microinvasion B–19 IPC with invasion	A–1 (micrometastasis in 1 node) B–2 (1 case showed macrometastasis in 1 node and 1 case showed isolated tumor cells in 3 nodes)	A–3 (2 pure IPC cases recurred as pure IPC 2 y and 8 y later. 1 patient further developed ipsilateral invasive lobular carcinoma. Third case recurred as invasive ductal carcinoma 8 y later) B–1	A–1 (1 pure IPC that recurred after 8 y further developed bone metastases 9 y later) B–0	A–None B–None Mean follow-up 72 mo (range, 3 to 209)	None of the patients who developed recurrence or metastasis received systemic hormonal treatment. A total of 5 patients had contralateral invasive ductal carcinoma
Total†	269/354	5	18	6	1	
SPC						
Maluf and Koerner[28] (not given)	A–4 SPC completely noninvasive B–16 SPC with invasion	A–None (0/1) B–None (0/11)	Not given	A–0 (0/4) B–1 patient with was lymph node negative SPC with invasion developed lung metastasis 6 y after diagnosis	Not given	It was not mentioned whether the lung metastasis was similar to SPC or to the associated carcinoma and whether the metastasis was papillary or not.
Tsang and Chan[50]	A–14 SPC B–20 SPC with invasion	—	A–1 (1/5 developed local recurrence at the sterna region as SPC 5 y after mastectomy) B–0 (0/7)	None	No BC related deaths up to 13 y follow-up	2 patients with SPC with invasion developed secondary primary tumor in the contralateral breast
Wei et al[54]	21 SPC with (7) or without (14) stromal invasion	None (0/16)	None (0/16)	None (0/16)	None (0/16)	

TABLE 2. (*continued*)

Study (Time Period)	PC Subtype	LN Status	Local Recurrences	DM	Breast Cancer-Related Death	Comments
Nassar et al[34] (1962-2004)	A–19 SPC with no invasion B–5 SPC and extravasated mucin (difficult to classify as pure SPC or SPC and invasive mucinous carcinoma) C–34 SPC with invasion	A–None (0/12) B–None (0/5)	A–None A–None C–6 cases	A–None B–1 case C–5 cases	A–0 (0/18) B–1 patient had SPC with signet-ring cell features and negative nodes died of metastatic signet-cell tumor after 10 y	Follow-up 5.7 y (range, 1-20 y). In 1 of SPC with invasion, lymph node metastasis showed morphology indistinguishable from SPC in the primary tumor
Otsuki et al[36]	A–5 SPC B–15 SPC with invasion	None	None	None	None	Mean follow-up time was 59 mo
Nicolas et al[35] (1997-2003)	A–2 pure SPC B–4 SPC with microinvasion C–5 SPC with invasion	A–None (0/1) B–1 (1/4; 2 nodes were positive with multiple small 2-3 mm foci with SPC morphology) C–None (0/2)	A–1 case developed invasive lobular carcinoma after 36 mo with no evidence of metastatic disease after 92 mo	No	None	In A and B, 4 patients had follow-up up to 96 mo with no evidence of metastasis or BC related deaths
Total†	67/164	1	2	1		

No skin fixation is reported in any of these studies.

*Mean size of none metastatic tumors was 1.9 cm while that of metastatic tumors was 3.5 cm. Stromal invasion was not identified in cases with metastasis but was found in 1 of 6 cases that showed local recurrences.

†Only pure PC or PC associated with DCIS or microinvasion included. Cases with coexisting invasive nonpapillary carcinomas were excluded.

statistically significant ($P < 0.001$). Although 8% of IPCs with follow-up data showed recurrences (31 of 357) compared with 3% of SPC (3 of 77), this difference was not significant ($P > 0.05$). Similarly, no difference between IPC and SPC regarding LN metastasis or DM was identified.

Although some studies reported that coexisting invasion[48] and recurrent disease[14,15] are associated with larger tumor size, other studies including this study did not find such an association.[14,24,48,55] Similarly, although some researchers have reported an association between either grade 3 PC or presence of associated conventional DCIS and presence of invasion,[25] recurrence, and metastasis,[6,15,25,48] no such associations were found in this study.

No association between stromal invasion by nodules and clusters of PC[15] or the presence of microinvasion in PC[58] and development recurrences or metastasis has been reported. In this study, stromal and skeletal muscle invasion is mainly seen in recurrent cases (8 cases, 3 of them showed LN micrometastasis and 1 showed VI). However, no subsequent event was reported for any of these patients; 1 patient died postoperatively, and 3 patients were alive with no further events 8 to 12 months after operation, whereas follow-up was not available in the other 4 patients.

In this study, 5 cases showed VI (2%). It has been reported that the epithelium of papillary lesions can be dislodged and displaced into the surrounding stroma, often in the needle tract, and even into adjacent lymphatic channels,[33] more frequently than other breast lesions (due to the inherent friability of papillary lesions).[40] However, in this study, 3 patients showed associated events; 2 had recurrent IPC, with 1 of them showing stromal invasion and LN positivity, and 1 patient had SPC with suspicion of invasion and showed LN positivity. These results, in addition to absence of VI in other cases, and despite earlier biopsy procedure, may support a biological mechanism for VI rather than mechanical displacement. None of the recurrent or metastatic cases was reported to show a peripheral layer of myoepithelial cells around primary PC, or to show LN positivity at initial presentation (even the 2 cases with nodal recurrences), and only 1 of 6 cases with DM showed stromal invasion at presentation.

Should EPC be Regarded as an In Situ or Invasive Carcinoma?

The role of myoepithelial cells in the identification of breast cancer invasion is well documented.[14,20,50] The demonstration of myoepithelial cells can help in differentiating papilloma from PC, as the former usually shows a continuous layer of myoepithelial cells at the interface between neoplastic epithelium and stroma in both the papillary fronds and at the periphery. Although papilloma overrun by DCIS and the majority of papillary DCIS show a continuous layer of myoepithelial cells at the peripheral tumor stromal interface,[20] approximately 85%

of EPCs show complete absence of myoepithelial cells at their peripheral stromal interface.[4,8,14,31,35,46,55] Although it has been suggested that ductal distension may be the reason for absence of myoepithelial cells at the periphery of EPC, myoepithelial cells are detected around benign papillary lesion of comparable size,[7] around adjacent foci of DCIS, and they are absent around small foci of EPC. In this study, all PCs with stromal and skeletal muscle invasion, VI, or LN metastasis showed complete absence of peripheral myoepithelial cells. Similarly, the only case of recurrent papillary DCIS with muscle invasion lacked peripheral myoepithelial cells. Although absence of myoepithelial cells suggests an invasive phenotype, it is only 1 step of the metastatic cascade, and the available data would argue that a substantial fraction of invasive tumors do not metastasize.[9,14,42,53] Microglandular adenosis, which is a notable example of a benign lesion that lacks myoepithelial cells and shows a yet unexplained diffuse infiltrative growth pattern, does not show evidence of metastasis.

The presence of a layer of a basement membrane around most EPCs cannot be regarded as evidence favoring an in situ carcinoma, as it has also been detected in a subset of invasive carcinomas[55] around nodal metastases mimicking DCIS[3,10,38] and, in this study, around invasive PC foci in the skeletal muscles and in the LN (Fig. 3B). Capsule formation is also discontinuous in a proportion of cases and absent around some foci of typical EPC[3,38,55] (Fig. 3A). Moreover, although PCs maintain their cystic or solid morphology in foci of obvious stromal/muscle invasion, this phenomenon has been reported in invasive carcinomas maintaining the morphologic appearance of DCIS even at metastatic sites that are sometimes referred to as revertant DCIS.[33]

Clinically, it is possible that local invasion may be related to tumor displacement,[14] and LN metastasis may be the result of synchronous separate occult invasive carcinomas[12] or tumor in ectopic tissue.[17,18,30,45] However, the number of cases showing stromal/muscle infiltration and VI in addition to local recurrence and occasional DM further support the invasive nature of these lesions. Although the presence of nodal metastases or invasive recurrences can be seen after an initial diagnosis of typical DCIS, the papillary growth pattern of some infiltrating/metastatic foci identical to the primary lesions supports the idea that this growth pattern can be seen in invasive carcinomas. The favorable clinical outcome of EPC does not provide direct evidence that these are in situ rather than invasive lesions, as some low-grade invasive carcinomas, such as adenoid cystic carcinomas, are associated with an equally favorable outcome.

Therefore, we agree with other researchers[18,55] that most EPCs are indolent invasive carcinomas, with a small proportion that may be in situ. The findings of previous studies highlight the difficulty in distinguishing in situ from invasive lesions.[9,32,37] As PC completely surrounded by myoepithelial cells cannot be considered as invasive carcinoma, we propose that myoepithelial markers be used in all papillary lesions and that (1) papillomas overrun by DCIS and papillary DCIS surrounded by myoepithelial cells are in situ lesions and should be treated in a similar manner as to conventional DCIS; (2) EPCs completely surrounded by a layer of myoepithelial cells are in situ lesions and should be named as PC in situ and treated akin to DCIS of similar grade and size; (3) PCs lacking a peripheral layer of myoepithelial cells should be regarded as a form of invasive tumor and should be referred to as EPC with omission of the word "in situ," and it should be recognized that adequate local control is the appropriate treatment; (4) results of this study and previous studies demonstrate that the outcome of pure EPC and EPC associated with microinvasion or suspicion of invasion are not different. In addition,

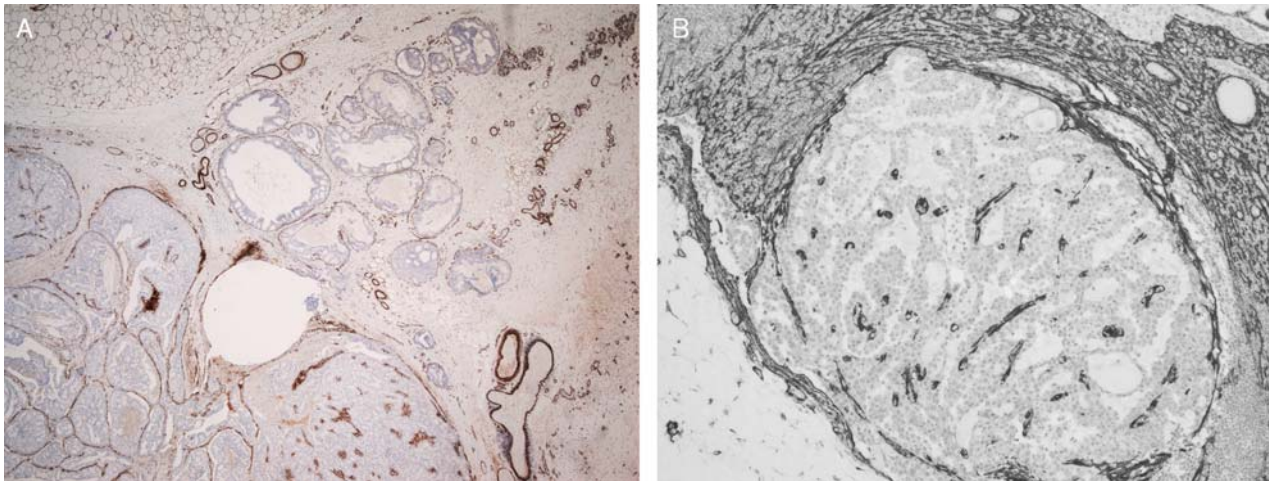

FIGURE 3. Collagen type 4 immunostaining: (A) A case of EPC showing discontinuous layer of collagen type 4 staining, which is absent around some foci. B, A case of metastatic EPC in the lymph node showing a peripheral layer of collagen type 4 staining around the metastatic papillary focus. full color online

histologically, there may be areas of sclerosis with entrapment of epithelial elements (as can be seen in benign papillomas). These entrapped areas, in addition to showing malignant cytology, lack myoepithelial cells akin to the main lesion and therefore, make interpretation of microinvasion difficult and of no practical significance; (5) PC associated with definite invasion by conventional non-PC should be typed based on the nonpapillary invasive component with the addition of the words "associated with PC" to explain the clinical presentation (ie, a mass) and its effect on whole tumor size estimation.[26] To avoid overstaging[11,21,29] and to ensure appropriate clinical management, only the size of the unequivocal nonpapillary invasive focus of carcinoma should be reported, whereas the size of PC should be added to the whole tumor size; and (6) adequate sampling of these lesions, particularly SPC, is also recommended to rule out an adjacent invasive carcinoma.

Available outcome data indicate that EPC seems to have an excellent prognosis with adequate local therapy alone. Incidence of local recurrence is low, and the incidence of DM or cancer-related death is extremely low, in accordance with those reported for pure DCIS.[11,15,29,48,52,55] Therefore, we believe that it is most prudent to continue to manage patients with these lesions similar to patients with DCIS and to avoid categorization of such lesions as a conventional form of invasive carcinoma.

No association between the rate of local or distant recurrence of EPC and the type of surgery (mastectomy or wide local excision with radiotherapy) has been reported.[4,15,24,28,34,55] Endocrine treatment should be considered for patients who are not fit for surgery and for patients with recurrent disease. In addition, cases associated with unusual morphologic high-risk features, such as signet-ring cell morphology[39] or invasive micropapillary carcinoma with lack of fibrovascular cores (unpublished observation), may have greater potential for benefit from use of systemic therapy. The tumor burden of the nodal metastatic deposits in a few cases, which showed nodal positivity and the absence of association between LN spread and tumor recurrences may challenge the value of LN sampling for primary EPC without coexisting conventional carcinoma and negative ultrasound of the axilla.

In conclusion, EPC lacking myoepithelial cells are a special type of invasive breast carcinoma with favorable prognosis. EPC showing an intact peripheral layer of myoepithelial cells should be regarded as in situ carcinomas. The term invasive PC should be abolished, and PC with coexisting conventional carcinoma should be named according to the nonpapillary component. EPC can be treated with adequate local therapy with or without hormonal therapy, as indicated in certain cases. The approach to LN sampling should be the same as for conventional DCIS.

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