Papillary Lesions of the Breast

An Update

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Objective.—To provide an overview focusing on the current concepts in the diagnosis and classification of papillary lesions of the breast incorporating recent molecular genetic advances.

Data Sources.—Data were obtained from pertinent peer-reviewed English-language literature.

Conclusions.—The recent evolution of molecular techniques has enhanced our knowledge of the pathogenesis of papillary carcinomas of the breast. This, along with emerging outcome studies, has led to prognosis-based reclassification of some of these entities. Additional studies focusing on the molecular signatures are needed to identify potential decision tools to further stratify these lesions with respect to prognostic significance.


Papillary lesions of the breast encompass a broad spectrum of neoplasms with respect to their clinical manifestation, histologic characteristics, and biological potential. The defining morphologic feature of these lesions is the presence of arborescent fibrovascular cores that support epithelial proliferation. Papillary lesions of the breast are exclusively intraductal neoplasms, although rarely an invasive carcinoma may rarely have a predominantly papillary architecture. Although histologically recognizing a lesion as papillary is typically not challenging, the histologic distinction of these entities is not always straightforward. Historically, different terminologies and variable criteria have been proposed for a given entity by various authorities. The difficulty in classifying these lesions has been further confounded by the scarcity of data and the heterogeneity across different studies with regard to the molecular genetic characteristics of this group of lesions.

The fibrovascular fronds, whereas its malignant counterpart lacks an intact myoepithelial cell layer within the papillae. Although histologically recognizing a lesion as papillary is typically not challenging, the distinction among the aforementioned entities is not always straightforward. In addition to the difficulty of diagnosing these lesions, different terminologies have been proposed by disparate authorities, and variable criteria have been suggested for a given entity. This article updates the current concepts in the diagnosis and classification of papillary lesions of the breast incorporating recent molecular genetic advances.

INTRADUCTAL PAPILLOMA

Intraductal papillomas are characterized by the presence of proliferating arborescent fibrovascular cores lined by an outer epithelial layer and an inner myoepithelial layer. They can be divided into central papilloma (large-duct papilloma) and peripheral papilloma (small-duct papilloma) owing to their distinct clinical manifestations and pathologic characteristics.1

Most papillomas are central in location. There is a wide age distribution but most tumors occur in individuals aged between 30 and 50 years.2 Central papillomas originate in the large ducts such as the segmental or subsegmental duct, and are typically solitary. They frequently present with serous or serosanguineous nipple discharge and, less commonly, a palpable mass. On imaging, central papillomas commonly display a solitary retroareolar mass in a dilated duct on mammography, intraluminal filling defect or duct dilatation on galactography, and a well-circumscribed,

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hypoechoic nodule or a smooth-walled cystic lesion with solid components on ultrasonography. On gross examination, central papillomas are often visible and appear as circumscribed nodules in a cystically dilated duct space. A papillary configuration may be appreciated in larger lesions, although they are more frequently bosselated or verrucous.

In contrast, peripheral papillomas arise in the terminal duct lobular units; thus, they are often clinically occult and discovered incidentally by mammographic calcifications or manifest as an enhancing mass on magnetic resonance imaging. Peripheral papilloma is also primarily a disease of middle-aged women. In contrast to central lesions, peripheral papillomas are typically grossly unidentifiable.

Histologically, the fibrovascular stalks of both types of intraductal papillomas are typically broad, although thin papillae may be seen in areas. An intervening myoepithelial cell layer invariably resides in the papillary fronds. The myoepithelial cells are typically apparent at higher magnification but may rarely be inconspicuous, thus necessitating immunohistochemical stains for myoepithelial markers such as p63, smooth muscle myosin heavy chain, and high-molecular-weight keratins (ie, cytokeratin [CK] 5/6, CK14, CK903/34βE12) (Figure 1, A through D).

The luminal epithelial component may comprise a single layer of columnar or cuboidal cells. However, a variable degree of epithelial proliferation is a frequent finding, which sometimes becomes so excessive that it obscures the papillary nature of the lesion, making it difficult to distinguish from its malignant counterpart. Florid ductal epithelial hyperplasia often shows a syncytial or streaming pattern with secondary, slitlike lumina or fenestrations characteristic of usual ductal hyperplasia. Broad-based micropapillae may also be present. The proliferating epithelial cells are typically heterogeneous and overlapping or irregularly spaced, and have indistinct cell borders and variably sized nuclei with frequent nuclear grooves and pseudonuclear inclusions (Figure 2, A and B). When in doubt, the nature of benign duct epithelial proliferation can be reaffirmed by a CK5/6 stain, which typically shows a patchy or mosaic staining pattern, unlike its malignant counterpart, which shows lack of CK5/6 expression. The p63 stain highlights only the myoepithelial cells and is negative in ductal epithelium, thus is most helpful in the context of evaluating fibrovascular cores (Figure 2, C and D).
**Figure 2.** Intraductal papilloma with epithelial hyperplasia. 

A. Intraductal papilloma with florid ductal epithelial hyperplasia. 

B. High-power view of epithelial hyperplasia demonstrates overlapping, heterogeneous cells forming secondary lumina, with frequent nuclear grooves and pseudoinclusions typical of usual ductal hyperplasia. 

C. An immunostain for cytokeratin 5/6 shows a patchy staining pattern in the proliferating epithelial cells in addition to its reactivity with basal myoepithelial cells. 

D. The p63 stain highlights only the myoepithelial cells and is negative in ductal epithelium. 

E. Intraductal papilloma with focal myoepithelial cell hyperplasia. 

F. A p63 stain highlights the proliferating myoepithelial cells in the lesion shown in E (hematoxylin-eosin, original magnifications ×100 [A] and ×200 [B and E]; original magnifications ×100 [C and D] and ×200 [F]).
Myoepithelial cell hyperplasia may be occasionally present (Figure 2, E and F). Focal apocrine metaplasia is frequently seen within intraductal papillomas but is almost always absent in intraductal papillary carcinomas, making it a useful adjunct in the differential diagnosis along with other features (Figure 3, A and B). Other reported metaplastic features include squamous, mucinous, clear cell, and sebaceous metaplasia. Collagenous spherulosis can involve papillomas. The associated tubular architecture in the background of proliferating epithelial cells may give rise to fenestrated pattern. Recognition of the intraluminal eosinophilic (or rarely basophilic) basement membrane material surrounded by flattened myoepithelial cells (as opposed to polarized columnar cells in cribiform DCIS) is crucial to avoid erroneous diagnosis (Figure 3, C and D).

Areas of hemorrhage or infarction are not uncommon findings in papillomas, especially in large and central lesions, either as a result of a needling procedure or torsion of fibrovascular stalks (Figure 3, E). Rarely, the entire lesion may be infarcted. In cases of no residual viable tissue, the tumor should be designated as an infarcted papillary lesion. Squamous metaplasia may be present more often in areas of infarction (Figure 3, F).

A variable amount of stromal fibrosis is another common finding associated with papillomas, especially in longstanding lesions. The fibrosis/sclerosis may occasionally become so extensive that it obliterates the underlying papillary configuration. These lesions have been known as sclerosing intraductal papillomas (Figure 4, A through C). Of note, microcalcifications are more commonly associated with these lesions. Sclerosing papillomas may present clinically as a palpable lump fixed to the skin, and radiographically as stellate, irregular speculated abnormalities, thus closely mimicking invasive carcinoma. By the same token, the compressed and distorted glandular structures in the background of extensively sclerotic and hyalinized stroma may histologically create a pseudoinfiltrative pattern that would mimic carcinoma, especially in core needle biopsy samples. In such cases, myoepithelial cells are usually discernible in at least some of the entrapped, irregularly shaped epithelial elements on routine hematoxylin-eosin-stained sections. In cases of ambivalence, immunohistochemical stains may be used to identify the persistent myoepithelial cells and resolve the uncertainty.

PAPILLOMA WITH ADH AND PAPILLOMA WITH DCIS

Some intraductal papillomas may have areas of atypical ductal epithelial proliferation that would fulfill the criteria for ADH or DCIS if observed outside of the context of a papillary lesion, more often in peripheral papillomas than those in the central location. These lesions are designated as papilloma with ADH and papilloma with DCIS, respectively. The atypical features include the presence of evenly spaced, small, regular cells with round, monotonous nuclei characteristic of those in ADH and low-grade DCIS, and complex architecture patterns (ie, solid, cribriform, or micropapillary) (Figure 5, A through C). These foci have evenly spaced, small, regular cells with round, monotonous orientation, and associated microcalcifications are more frequently found in intraductal papillary carcinomas when compared with benign papillomas. The presence of any of these sonographic observations gives a sensitivity and specificity of 85.7% and 64.9%, respectively, for detection of malignant papillary lesions. There are no distinguishable macroscopic features.

Histologically, intraductal papillary carcinomas characteristically show variably dilated ductal-lobular luminal spaces filled with slender or branching fibrovascular stalks lined by stratified columnar neoplastic epithelial cells. The papillae are typically thin and delicate with minimal stromal fibrosis.

At present, there are no universally accepted criteria as to the distinction between papilloma with ADH and papilloma with DCIS. A 3-mm cutoff based on the extent of the lesion has been proposed; a tumor with the atypical epithelial proliferation 3 mm or smaller is diagnosed as papilloma with ADH, whereas that with the atypical focus larger than 3 mm is designated as papilloma with DCIS. Other authors have suggested a 30% cutoff based on the proportion of atypical epithelial proliferation, later revised to 90%, as the clinical behaviors do not seem to differ when comparing tumors with atypical areas less than a third of the lesion and those with at least a third but less than 90% of the lesion displaying such changes. Of note, none of the papillary lesions were found to have atypical foci that occupied more than 65% to 70% of the tumor. The World Health Organization Working Group is of the view that the extent-/size-based criteria rather than proportion criteria should be used in routine practice. It is important to emphasize that when the atypical epithelial proliferation is of intermediate or high nuclear grade, a diagnosis of papilloma with DCIS should be rendered regardless of its quantity, an approach adapted from the conventional criteria for differentiating ADH and DCIS in intraductal proliferative lesions without papilloma. Moreover, the presence of DCIS in neighboring breast tissue is particularly supportive of the diagnosis of DCIS within a papilloma.

Papillomas with DCIS should be distinguished from intraductal papillary carcinoma (see subsequent text). The latter is thought to be a de novo in situ malignant process by some authors, and thus more significant in predicting the patient’s risk of subsequent invasive disease. Nonetheless, the prognosis of papilloma with DCIS after complete excision remains unclear, and is thought to be equivalent to that of ADH. This is in contrast to that of intraductal papillary carcinoma, which is similar to DCIS in general. The presence of multiple atypical papillomas is reportedly associated with a much higher risk of subsequent invasive carcinoma.

INTRADUCTAL PAPILLARY CARCINOMA

Intraductal papillary carcinoma, also known as papillary DCIS and noninvasive papillary carcinoma, is distinguished by the complete or near-complete absence of myoepithelial cells in the papillary fronds of the intraductal neoplastic proliferation. Nipple discharge or a palpable mass may be the presenting symptom, depending on the location and size of the lesion.

These lesions may appear as an irregular intraductal/intracystic mass with increased vascularity on imaging studies, or present with mammographic calcifications as other DCIS subtypes. Ultrasonographically, a nonparallel orientation, an echogenic halo, posterior acoustic enhancement, and associated microcalcifications are more frequently found in intraductal papillary carcinomas when compared with benign papillomas. The presence of any of these sonographic observations gives a sensitivity and specificity of 85.7% and 64.9%, respectively, for detection of malignant papillary lesions. There are no distinguishable macroscopic features.

Histologically, intraductal papillary carcinomas characteristically show variably dilated ductal-lobular luminal spaces filled with slender or branching fibrovascular stalks lined by stratified columnar neoplastic epithelial cells. The papillae are typically thin and delicate with minimal stromal fibrosis.
Figure 3. Various appearances of intraductal papilloma. A, Focal apocrine metaplasia is frequently present in benign papillomas but is almost always absent in malignant lesions. B, The proliferating epithelial cells with apocrine metaplasia are negative for cytokeratin 5/6, thus are not to be confused with intraductal papillary carcinoma. C, Collagenous spherulosis involving a papilloma may give rise to an appearance of a cribriform ductal carcinoma in situ on low-power view. D, Higher magnification shows tubular structures containing intraluminal basement membrane material surrounded by flattened myoepithelial cells in collagenous spherulosis. E, Papilloma with infarction. F, Papilloma with squamous metaplasia (hematoxylin-eosin, original magnifications ×40 [A, C, and E] and ×200 [D and F]; original magnification ×100 [B]).
when compared with those of intraductal papillomas. Scant myoepithelial cells may be present within the papillae or in the epithelial proliferation, but an intact myoepithelial cell layer is absent.\textsuperscript{19-21} As with other morphologic types of DCIS, a myoepithelial cell layer is retained at the periphery of the involved duct wall, thus defining the in situ nature of the lesion. However, the peripheral myoepithelium may be attenuated or discontinuous in larger lesions with markedly distended duct spaces (Figure 6, A).\textsuperscript{22,23} A dimorphic population of malignant cells reportedly occurs in up to one-quarter of cases, in which the second population consists of cells with clear cytoplasm, often in a basal location, and thus may be confused with myoepithelial cells, resulting in potential erroneous diagnosis (Figure 6, B).\textsuperscript{24} Proliferation of neoplastic epithelial cells may produce additional architectural patterns such as solid, cribriform, and micropapillations, which, when extensive, may obliterate the spaces between the papillae (Figure 6, C). The cytologic features of the lesional cells are typically those of low- or intermediate-grade DCIS, although rare high-grade lesions do exist. Another pitfall is that the endothelial cells juxtaposed to the neoplastic epithelial cells in the papillary fronds may be mistaken for myoepithelial cells. When in doubt, immunohistochemical staining for myoepithelial markers can be used to reach a decisive diagnosis (Figure 6, D). It should be noted that some myoepithelial markers, such as smooth muscle actin and calponin, variably cross-react with stromal fibroblasts, vessel pericytes, and endothelial cells, and thus have minimal utility in the characterization of papillary lesions.\textsuperscript{25} Thus, p63 and high-molecular-weight keratins (CK5/6, CK14, 34\(\beta\)E12/CK903) are better markers to illustrate the presence/absence of myoepithelial cells in this setting. The neoplastic epithelial cells are negative for high-molecular-weight keratins,\textsuperscript{26} and typically show strong estrogen receptor (ER) and progesterone receptor (PR) expression.

The pathogenesis of intraductal papillary carcinoma remains a matter of debate. As previously mentioned, these lesions have been regarded as a de novo malignant papillary epithelial proliferation by some authorities.\textsuperscript{13} Others have argued that they substitute a malignant neoplastic population resulting from a gradual transformation and replacement of a preexisting benign papilloma.\textsuperscript{27} With regard to the genetic characteristics, studies demonstrating molecular differences between benign and malignant papillary lesions are few and suffer from limited samples. Loss of heterozygosity of 16q23 was found only in malignant papillary lesions, whereas loss of heterozygosity at loci 16p13 and 16q21 was detected in both benign and malignant lesions.\textsuperscript{28} Loss of heterozygosity at the TP53 locus was also found to be significantly associated with a malignant phenotype. Another limited study showed an overall lower frequency of activating point mutations of \(PIK3CA\), \(AKT1\), and \(NRAS\) genes in papillary carcinomas when compared with benign papillomas.\textsuperscript{29} Thus, molecular characteristics appear heterogeneous, and additional studies are needed to further delineate the molecular origins of these papillary lesions.

\section*{ENCAPSULATED (INTRACYSTIC) PAPILLARY CARCINOMA}

Encapsulated papillary carcinoma is morphologically similar to intraductal papillary carcinoma with the exception that the myoepithelial cells are absent at the surrounding thick fibrous capsule. These lesions have been traditionally regarded as a
Figure 5. Papilloma with atypical ductal hyperplasia (ADH)/ductal carcinoma in situ (DCIS). A, A papilloma with areas of monotonous cellular proliferation. B, A cytokeratin 5/6 (CK5/6) stain in the lesion shown in A demonstrates lack of a mosaic staining pattern in the proliferating cells, thus rendering it a papilloma with DCIS according to the extent/size-based criteria, given the area of interest is greater than 3 mm. C, A sclerosing papilloma with ADH showing focal cellular proliferation with small, round, uniform, and evenly spaced nuclei characteristic of those in ADH and low-grade DCIS. D, Papilloma with DCIS showing prominent squamous differentiation. E, The neoplastic cells shown in D are strongly immunoreactive with CK5/6. F, A p63 stain highlights rare myoepithelial cells in the lesion shown in D (hematoxylin-eosin, original magnifications ×20 [A], ×100 [C], and ×200 [D]; original magnifications ×40 [B] and ×200 [E and F]).
variant of DCIS by most authorities given their discrete nodular growth, lack of stromal reaction, and indolent clinical behavior, and further supported by the presence of moderate to intense collagen type IV expression surrounding the lesion. This notion has been challenged by others who propose that the tumor represents an indolent form of invasive carcinoma with an expansile growth pattern, as the absence of peripheral myoepithelium argues against the current concept of an in situ carcinoma. The latter proposal has been further supported by the finding of occasional lymph node and distant metastasis associated with these lesions.

Encapsulated papillary carcinoma frequently occurs in elderly patients, with an average age of 65 years. The tumor often presents as a retroareolar well-defined mass on mammography, and a cystic lesion with solid components on ultrasound. On gross examination, it commonly appears as a circumscribed friable mass within a cystic cavity, and hence is also termed intracystic papillary carcinoma.

Histologically, one or more well-circumscribed nodular masses within a cystically dilated duct surrounded by a thick fibrous capsule are typically evident on low-power magnification (Figure 7, A). The duct spaces are filled by slender fibrovascular stalks devoid of myoepithelial cells. The papillary fronds are lined by neoplastic epithelial cells with low- or intermediate-grade nuclei, although high nuclear grade may rarely be observed. The neoplastic cells typically show strong ER and PR expression.

A layer of myoepithelial cells is absent at the periphery of the lesion on routine hematoxylin-eosin–stained sections as well as with immunohistochemistry (Figure 7, B). The periphery may sometimes be lined by spindled cells that show identical nuclear features to those in the papillary fronds, in contrast to myoepithelial cells that typically exhibit flat, cuboidal, or rounded nuclei (Figure 7, C and D). Rarely, the lining cells may take on a columnar cell appearance that contains subnuclear vacuoles and shows reverse polarity, thus simulating piano keys. Again, the epithelial/non-myoeplithelial nature of these lining cells can be confirmed.
Figure 7. Encapsulated papillary carcinoma. A, The tumor often presents with one or more well-circumscribed nodular masses within a cystically dilated duct. B, The tumor nodule is surrounded by a thick fibrous capsule with variable degree of chronic inflammation. C, The periphery may be lined by stratified epithelial cells similar to those in the papillary fronds, in contrast to myoepithelial cells lining the periphery of benign papillomas that are typically flattened, cuboidal, or rounded. D, A cytokeratin 5/6 stain confirms the absence of myoepithelial lining at the periphery of the encapsulated papillary carcinoma shown in C, whereas it highlights the myoepithelial cells in the adjacent papilloma. E, The peripheral lining cells of encapsulated papillary carcinoma may rarely take on the appearance of piano key–like columnar cells with subnuclear vacuoles and reverse polarity. F, The nonmyoepithelial nature of the lining cells shown in E is demonstrated by p63 immunostaining (hematoxylin-eosin, original magnifications ×20 [A], ×100 [B and C], and ×400 [F]; original magnifications ×200 [D] and ×400 [F]).
by immunostaining for myoepithelial markers (Figure 7, E and F).

In the absence of DCIS or conventional invasive carcinoma in the surrounding breast tissue, encapsulated papillary carcinoma has a favorable prognosis with adequate local therapy alone.34,37-39 The presence of concurrent DCIS in the adjacent breast tissue is reportedly associated with a higher risk of local recurrence.40 However, a small proportion of encapsulated papillary carcinomas may be associated with frankly invasive carcinoma. The invasive component is typically of no special type, with no papillary features. Given the controversies regarding the classification of this entity, there is no universal agreement on how to stage encapsulated papillary carcinoma at this time. It is generally accepted that in the presence of conventional invasive carcinoma, the tumor should be staged based on the size of the invasive component only, in order to prevent overtreatment. Despite their ability to rarely metastasize, the general consensus is that in the absence of unequivocal invasive carcinoma, such lesions should be staged and managed as DCIS given their indolent clinical course and good prognosis.5,13,30

A high-resolution microarray-based comparative genomic hybridization analysis of encapsulated papillary carcinoma with concurrent DCIS and invasive carcinoma showed that the 3 components could not be separated into different clusters; the former had the greatest number of genomic copy number aberrations, followed by DCIS and invasive carcinoma.41 Based on the overall molecular changes, it was suggested that encapsulated papillary carcinoma was closer to DCIS than to invasive carcinoma. Given the small number of cases analyzed in these studies, additional molecular analyses are needed to further characterize these lesions.

SOLID PAPILLARY CARCINOMA

The term solid papillary carcinoma was initially introduced to describe a variant of intraductal papillary carcinoma that grows in a solid papillary pattern, displays low-grade cytologic features, and often has neuroendocrine differentiation as well as intracellular or extracellular mucin production.42 The tumor usually presents as a well-defined mass on imaging studies.35,36 Grossly, solid papillary carcinoma may be seen as a fleshy, firm or soft, well-circumscribed nodular mass with a tan-white or yellowish brown appearance.21 These lesions occur mostly in elderly women, with a mean age in the seventh decade of life.43 Microscopically, solid papillary carcinomas are characteristic seen as multiple solidified circumscribed nodules, and lack cribriform or discrete papillary architecture on low-power view (Figure 8, A).42 However, the delicate underlying fibrovascular stromal network devoid of a myoepithelial cell layer is typically discernible at higher magnification. The densely cellular neoplastic cells often appear to be streaming, and thus may be mistaken for intraductal papilloma with florid ductal hyperplasia.44 When in doubt, the absence of staining for high-molecular-weight keratin (ie, CK5/6) is of diagnostic value (Figure 8, B and C). Intracellular and/or extracellular mucin production is not uncommon (Figure 8, D). The proliferating tumor cells are typically bland and cohesive, have oval or spindled nuclei, and exhibit low to intermediate nuclear grade (Figure 8, E). The fibrovascular cores can be variably collagened, with peripheral palisading of tumor cells forming perivascular pseudorosettes. The lesional cells often demonstrate neuroendocrine features, including finely granular eosinophilic cytoplasm and salt-and-pepper nuclei (Figure 8, F).42 In fact, immunoreactivity for neuroendocrine markers with variable intensity and spatial distribution has been reportedly observed in at least half of the cases.45,46 Mitotic figures are visible, but not brisk and with no atypical forms.

The tumor is historically considered a distinct form of DCIS as the circumscribed tumoral nests appear noninvasive and many lesions demonstrate peripheral myoepithelial cell lining.42 However, an absence of myoepithelial cell layers at the periphery of the solid tumor nodules has been demonstrated by immunohistochemical analysis in subsequent studies (as demonstrated in Figure 8, B). This raises the possibility that many of these lesions may represent invasive carcinomas with a pushing-border and expansile growth pattern rather than variants of DCIS, as with encapsulated papillary carcinoma.47,48 This is further complicated by the finding that an intact myoepithelial cell layer may be seen in some of the tumoral nests within a lesion (as shown in Figure 8, C).13,47 Therefore, similar to encapsulated papillary carcinoma, a precise classification of these lesions has been controversial. Nonetheless, given that in the absence of conventional invasive carcinoma, these tumors have an indolent clinical course similar to that of DCIS,42,48 the general consensus is that these lesions should be regarded as in situ carcinoma for staging purposes.43 Metastases from such tumors are rare but do occur.47

The nodules of solid papillary carcinoma frequently have a geographic jigsaw pattern and irregular peripheries, thus suggesting invasion. In some lesions, such areas may blend into conventional invasive carcinoma (Figure 9, A). The coexisting invasive component is frequently mucinous carcinoma or carcinoma with endocrine features,42 although other histologic types of carcinoma may also be seen (Figure 9, B).45,46 Moreover, the cells of solid papillary carcinoma typically show strong ER and PR expression, and lack HER2 overexpression/gene amplification. When an invasive carcinoma is coexistent, it usually retains the same receptor expression profile.48

Rarely, solid papillary carcinoma and encapsulated papillary carcinoma may present as a composite tumor coexisting within one tumor nodule, thus giving the appearance of one tumor growing into the other (Figure 10, A through C).49 This observation raises the interesting possibility of a common pathway of carcinogenesis for these 2 unique variants.

Given the challenge in stratifying intraductal papillary lesions, an algorithmic approach has been proposed to the diagnosis, in which the presence and distribution of myoepithelial cells is first determined, followed by characterization of the nature of the epithelial component with the judicious application of immunohistochemistry.53 Recent studies have shown that this algorithmic approach has a superior diagnostic utility when it is applied in adjunct to the use of an antibody cocktail consisting of low- and high-molecular-weight cytokeratins and p63, especially on needle biopsy specimens.50,51 The salient histologic and immunophenotypic features of intraductal papillary lesions are summarized in the Table.

INVASIVE PAPILLARY CARCINOMA

The term invasive papillary carcinoma should be reserved for invasive adenocarcinomas with an exclusively (>90%) papillary histomorphology (Figure 11, A and B).52 Pure invasive papillary carcinoma is extremely rare, with a reported incidence of approximately 0.5% of all invasive breast cancers
Figure 8. Solid papillary carcinoma. A, Multiple solid, circumscribed nodules without apparent papillary architecture are characteristic on low-power view. B, The absence of peripheral myoepithelium is demonstrated by a cytokeratin 5/6 (CK5/6) stain, which highlights the myoepithelial cells in the adjacent normal duct. C, An intact myoepithelial cell layer may be seen in some of the tumoral nests as confirmed by this CK5/6 stain. D, Mucin production is not uncommon in solid papillary carcinoma. E, The neoplastic cells typically have low- to intermediate-grade oval or spindled nuclei. F, The lesional cells often exhibit neuroendocrine features, with granular eosinophilic cytoplasm and salt-and-pepper nuclei, and form perivascular pseudorosettes in the variably collagenized fibrovascular cores (hematoxylin-eosin, original magnifications ×40 [A], ×100 [D], ×200 [E], and ×400 [F]; original magnification ×40 [B and C]).
in some series. However, the studies in the literature often do not clearly distinguish in situ and invasive papillary carcinomas. For this reason, the epidemiologic and clinical characteristics of this rare tumor type have not been well defined. There are no specific features on imaging studies. The only notable differential sonographic finding between noninvasive and invasive papillary carcinoma is a circumscribed margin.

It should be noted that an invasive nonpapillary carcinoma arising from encapsulated or solid papillary carcinoma should not be categorized as invasive papillary carcinoma. Further, invasive micropapillary carcinoma should not be confused with invasive papillary carcinoma. The former represents a separate special tumor type characterized by cohesive clusters or nests of neoplastic cells devoid of true fibrovascular cores, surrounded by empty spaces. This subtype frequently presents with lymphovascular invasion and lymph node metastasis, and thus is associated with a dismal prognosis. Furthermore, papillary metastases from other anatomic sites, particularly ovary and lung, should be always included in the differential diagnosis (Figure 11, C and D).

Figure 9. Solid papillary carcinoma merged with invasive carcinoma. A, The nodules of solid papillary carcinoma merge with invasive carcinoma (lower left). B, The neuroendocrine differentiation is demonstrated by an immunostain for synaptophysin in this invasive carcinoma arising from a solid papillary carcinoma (hematoxylin-eosin, original magnification ×40 [A]; original magnification ×100 [B]).

Figure 10. Composite encapsulated papillary carcinoma and solid papillary carcinoma. A, A low-power view shows a tumor with 2 distinct morphologies characteristic of encapsulated papillary carcinoma and solid papillary carcinoma. B, The absence of myoepithelium within the papillae and at the periphery of both components is demonstrated by this cytokeratin 5/6 immunostaining. C, The 2 components intermingle in one tumor nodule, imparting the appearance of one tumor growing into the other (hematoxylin-eosin, original magnifications ×40 [A] and ×100 [C]; original magnification ×200 [B]).
### Salient Histologic and Immunophenotypic Features of Intraductal Papillary Lesions

<table>
<thead>
<tr>
<th>Entity</th>
<th>Papillae</th>
<th>Apocrine Metaplasia</th>
<th>MEC Within the Papillae</th>
<th>MEC at the Periphery</th>
<th>CK5/6 in Neoplastic Cells</th>
<th>p63 in Neoplastic Cells</th>
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<tbody>
<tr>
<td>Papilloma</td>
<td>Typically thickened fibrovascular cores, may be sclerosed or infarcted</td>
<td>Frequently present</td>
<td>Present</td>
<td>Present</td>
<td>Patchy/mosaic staining in hyperplastic cells; negative in cells with apocrine metaplasia</td>
<td>Absent</td>
</tr>
<tr>
<td>Papilloma with ADH/DCIS</td>
<td>Delicate in areas of ADH/DCIS</td>
<td>May be present</td>
<td>Absent in areas of ADH/DCIS</td>
<td>Present</td>
<td>Absent in areas of ADH/DCIS</td>
<td>Absent</td>
</tr>
<tr>
<td>Papillary DCIS</td>
<td>Typically delicate</td>
<td>Absent</td>
<td>Absent</td>
<td>Present</td>
<td>Absent in areas of ADH/DCIS</td>
<td>Absent</td>
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<tr>
<td>Encapsulated papillary carcinoma</td>
<td>Delicate</td>
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<td>Absent</td>
<td>Absent</td>
<td>Absent in areas of ADH/DCIS</td>
<td>Absent</td>
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<tr>
<td>Solid papillary carcinoma</td>
<td>Delicate, may be obscured</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent or focally present</td>
<td>Absent in areas of ADH/DCIS</td>
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Abbreviations: ADH, atypical ductal hyperplasia; CK5/6, cytokeratin 5/6; DCIS, ductal carcinoma in situ; MEC, myoepithelial cells.

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**Figure 11.** Invasive papillary carcinoma and metastatic papillary carcinoma. A, An invasive tumor showing an exclusive papillary growth pattern. B, A higher magnification demonstrating the fibrovascular cores. C, A core needle biopsy from a breast mass in a patient with a history of serous carcinoma of the ovary. D, A PAX8 stain delineates the ovarian origin of the tumor shown in C (hematoxylin-eosin, original magnifications ×40 [A and C] and ×100 [B]; original magnification ×100 [D]).

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A recent microarray-based comparative genomic hybridization analysis revealed that papillary carcinomas as a group displayed similar patterns of gene copy number aberrations when compared with grade- and ER-matched invasive carcinoma of no special type. Further, the genomic profiles of encapsulated, solid, and invasive papillary carcinomas were remarkably similar, thus suggesting that papillary carcinomas may be best positioned as part of the spectrum of ER-positive breast cancers, rather than as a distinct entity.

However, the limited sample size and the incomplete follow-up information render the comparisons among subtypes of papillary carcinomas exploratory and hypothesis generating.

**EPITHELIAL DISPLACEMENT: A PAPILLARY PHENOMENON**

Mechanical displacement of epithelium may occur following a variety of needling procedures, including core needle biopsy, fine-needle aspiration, anesthetic injection, suture placement, and wire localization. In more than 90% of cases, artifactual epithelial displacement occurs in association with underlying papillary neoplasms (including pure intraductal papillomas), as these lesions are inherently friable. It is of exceptional importance to be aware of its occurrence and to recognize it histologically, as the displaced epithelium may produce a pattern closely simulating an invasive carcinoma and may result in a mistaken diagnosis in patients with benign lesions or in situ carcinoma.

Iatrogenic epithelial displacement almost always occurs in the biopsy site and needle tract, and is typically present in the form of isolated, small fragments of epithelium in artificial spaces within the mammary stroma. Caution should be exercised when small epithelial aggregates are present in traumatized breast stroma in the absence of a prior diagnosis of invasive carcinoma. These epithelial cell clusters are typically associated with a spectrum of biopsy site changes such as organizing hemorrhage, acute and chronic inflammation, foreign body reaction (ie, foamy histiocytes, giant cells, cholesterol clefts), fat necrosis, hemosiderin deposition, granulation tissue, or scarring, depending on the time from needling to surgical procedure (Figure 12, A through C). The absence of associated myoepithelial cells in the epithelial clusters is not, by itself,
sufficient for a diagnosis of invasive carcinoma, especially in the setting of papillary lesions. Definitive invasion should be concluded only in the context of concurrent desmoplastic stromal reaction, and in an area away from the previous needling procedure. Epithelial displacement residing in breast stroma outside a biopsy tract is rare and can be more problematic. However, the displaced epithelium typically does not evoke a stromal reaction, in contrast with true invasion.

The epithelium can also be displaced into lymphatic or vascular channels, and may rarely be seen in the initial core needle biopsy tissue.62,64,65 In the absence of unequivocal invasive carcinoma, the presence of epithelial clusters in the lymphovascular spaces should be interpreted with utmost caution. When the focus is limited to the biopsy site, epithelial displacement should be considered in the differential diagnosis.

Further, single or small clusters of epithelial cells can also be found in the regional lymph nodes in the absence of bona fide invasive carcinoma, and thus may cause more diagnostic confusion (Figure 12, D).63,66 Hypothetically, regional lymph nodes drain traumatized areas as part of the tissue healing process regardless of their contents, as with silicon lymphadenopathy. Moreover, breast massage in women undergoing sentinel lymph node biopsy may also cause epithelial displacement to lymph nodes.67 In this regard, nuclear features of the epithelial cells in the lymph node may provide pertinent information with respect to benign or malignant origin, as the latter are typically larger and pleomorphic.68 In cases of malignant-appearing epithelium and pleomorphic.66 In cases of malignant-appearing epithelium and pleomorphic.66

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Lastly, the biologic fate of displaced epithelium in all sites remains to be determined. Appropriate documentation and long-term clinical follow-up are needed to determine the clinical significance of this unique phenomenon.

SUMMARY

Papillary lesions of the breast represent a heterogeneous group of neoplasms sharing many morphologic similarities. These lesions may demonstrate overlapping clinical and radiologic features but may have diverse clinical outcomes. Our state-of-the-art knowledge has led to outcome-based reclassification of some of these entities. Further studies are needed to elucidate the pathogenesis and, more importantly, to seek potential decision tools in stratifying these lesions given the divergent approaches currently used.

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References
33. Mulligan AM, O'Malley FP. Metastatic potential of encapsulated (intra-
cystic) papillary carcinoma of the breast: a report of 2 cases with axillary lymph
34. Solorzano CC, Middleton LP, Hunt RK, et al. Treatment and outcome of
35. Knelson MH, el Yussef SJ, Goldberg RE, Ballance W. Intracystic papillary
carcinoma of the breast: mammographic, sonographic, and MR appearance with
36. Schneider JA. Invasive papillary breast carcinoma: mammographic and
38. Harris KP, Faliakou EC, Exon DJ, Nasiri N, Sacks NP, Gui GP. Treatment
86(10):1274.
(encycled) papillary carcinoma of the breast: a clinical, pathological, and
40. Carter D. Intraductal papillary tumors of the breast: a study of 78 cases.
interrelationship with in situ and invasive carcinoma and a proposal of
pathogenesis: array comparative genomic hybridization study of 14 cases. Mod
42. Maluf HM, Koerner FC. Solid papillary carcinoma of the breast: a form
of intraductal carcinoma with endocrine differentiation frequently associated
43. Visscher D, Collins LC, O’Malley F, Barde S, Reis-Filho JS. Solid papillary
WHO Classification of Tumours of the Breast. Lyon, France: IARC Press; 2012;
44. Rabban JT, Koerner FC, Lerwill MF. Solid papillary ductal carcinoma in situ
versus usual ductal hyperplasia in the breast: a potentially difficult distinction
46. Tan PH, Lui GG, Chiang G, Yap WM, Poh WT, Bay BH. Ductal carcinoma in
situ with spindled cells: a potential diagnostic pitfall in the evaluation of breast
47. Nicolas MM, Wu Y, Middleton LP, Gilcrease MZ. Loss of myoepithelium is
variable in solid papillary carcinoma of the breast. Histopathology. 2007;51(5):
657–665.
48. Nassar H, Qureshi H, Adsad NV, Visscher D. Clinicopathologic analysis of
solid papillary carcinoma of the breast and associated invasive carcinomas. Am J
49. Cui X, Wei S. Composite encapsulated papillary carcinoma and solid
papillary carcinoma. Pathol Int. 2014;64(3):133–137.
50. Reisenbichler ES, Balmer NN, Adams AL, Hameed O. Luminal
cytokeratin expression profiles of breast papillomas and papillary carcinomas and
the utility of a cytokeratin 5/6/3/4 antibody cocktail in their distinction. Mod Pathol.
51. Reisenbichler ES, Adams AL, Hameed O. The predictive ability of a CK5/
p63/CK8/18 antibody cocktail in stratifying breast papillary lesions on needle
779.
52. Tse G, Moriya T, Niu Y. Invasive papillary carcinoma. In: Lakhani SR, Ellis
IO, Schnitt SJ, Tan PH, van de Vijver MJ, eds. WHO Classification of Tumours of
analysis of invasive micropapillary differentiation in breast carcinoma. Mod Pathol.
2001;14(9):836–841.
54. Walsh MM, Bleiweiss IJ. Invasive micropapillary carcinoma of the breast:
55. Duprez R, Wilkerson PM, Lacroix-Triki M, et al. Immunophenotypic and
genomic characterization of papillary carcinomas of the breast. J Pathol. 2012;
226(3):427–441.
56. Youngson BJ, Cranor M, Rosen PP. Epithelial displacement in surgical
896–903.
57. Lee KC, Chan JK, Hu LC. Histologic changes in the breast after fine-needle
58. Youngson BJ, Liberman L, Rosen PP. Displacement of carcinomatous
epithelium in surgical breast specimens following stereotactic core biopsy. Am J
59. Bleiweiss IJ, Naji CS, Jaffer S. Axillary sentinel lymph nodes can be falsely
positive due to iatrogenic displacement and transport of benign epithelial cells in
60. Naji C, Bleiweiss I, Jaffer S. Epithelial displacement in breast lesions: a
61. Pathologic changes secondary to diagnosis or treatment of carcinoma. In:
Hameed O, Wei S, Desouki MM, Umphrey H, eds. Advances in Surgical
62. Diaz NM, Mayes JR, Vrcel V. Breast epithelial cells in dermal
angiolymphatic spaces: a manifestation of benign mechanical transport. Hum
63. Koo JS, Jung WH, Kim H. Epithelial displacement into the lymphovascular
space can be seen in breast core needle biopsy specimens. Am J Clin Pathol.
64. van Deuzen CH, Bult P, de Boer M, et al. Morphometry of isolated tumor
cells in breast cancer sentinel lymph node metastases or displacement? Am J
1645.