Diagnostic challenges in papillary lesions of the breast

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Summary

Papillary lesions of the breast comprise a heterogeneous group of diseases ranging from benign and atypical lesions to malignant tumours including non-invasive and invasive entities. Although diagnosis of papillary lesions featuring typical histological features is straightforward, a proportion shows overlapping features, posing diagnostic challenges. In addition to being uncommon, the excellent behaviour of papillary tumours reduces the distinguishing value of individual histological features and increases the subjectivity of interpretation of various diagnostic features. Therefore the overall categorisation, which is based on a constellation of subjective features, may vary with subsequent management implications. Concordance studies revealed that recognition of papillary carcinomas (PC) as a malignant entity by pathologists is high, but concordance of its classification into *in situ* and invasive disease can be problematic, as can assessment of prognostic and predictive factors in the invasive component. Identification of low nuclear grade atypia within benign papillary lesions and its classification into atypia or *in situ* carcinoma may also pose a diagnostic challenge. Although immunohistochemistry is helpful in evaluation of benign and atypical lesions it has a limited utility in differentiating the majority of PC as non-invasive or invasive disease. Pathologists should be aware of the various entities and the differential diagnosis of each entity, the existence of lesions with overlapping features and should follow the updated guideline recommendation for their diagnosis and management. These rare lesions usually require additional diagnostic work-up and difficult cases should trigger consensus opinion or expert referral.

Key words: Breast cancer; papillary lesions; diagnosis; challenges.

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INTRODUCTION

Papillary lesions of the breast are a heterogeneous group of diseases characterised by the presence of epithelial proliferation supported by fibrovascular cores. The presence of these fibrovascular cores is generally accepted as the hallmark of papillary lesions in the breast. Breast lesions featuring small papillary-like projections lacking fibrovascular cores are designated as micropapillary. Papillary lesions arise within the ducto-lobular system of the breast and typically show a cystic structure but solid forms occur, resulting from florid epithelial proliferation.^{1–5} Although this solid pattern of

growth can be seen in intraductal papilloma and encapsulated papillary carcinoma (EPC) (Fig. 1), it is the predominant growth pattern in solid papillary carcinoma (SPC).^{1–6} Clinical evidence indicates that breast carcinomas featuring predominant papillary morphology are associated with better outcome compared to their non-papillary counterparts including grade matched tumours.^{5–9}

Papillary lesions of the breast can broadly be classified into several types based on the following. (1) Location in the duct system. Papillary lesions can arise from large ducts or small ducts (terminal duct lobular units; TDLU). Large duct papillary lesions are typically solitary, present as a mass lesion or nipple discharge and include solitary papilloma, EPC and SPC. TDLU lesions include multiple papillomas and papillary ductal carcinoma *in situ* (DCIS) and these often present as calcification or an incidental finding associated with other lesions. (2) Nature of the proliferating epithelial cells. This can be hyperplastic in papilloma, neoplastic in papillary carcinoma (PC) or a mix of hyperplastic and neoplastic in papilloma involved by atypical proliferation. The presence of cellular differentiation such as neuroendocrine and mucinous changes can be used to differentiate EPC from SPC, while on rare occasions the degree of cytonuclear atypia in PC can also be used to differentiate *in situ* from invasive disease for management purposes¹⁰ (see below). (3) Presence of and location of myoepithelial cells (ME). This not only helps in distinguishing benign from malignant papillary lesions but can also differentiate specific subtypes of malignant papillary lesions (Table 1). (4) Morphology of PC. PC including EPS and SPC featuring a well-circumscribed margin with or without peripheral fibrous capsule are considered as non-invasive (*in situ*) disease for management purposes. PC featuring irregular outlines with ragged edge and complex jigsaw pattern of growth in SPC, or focal areas of irregular stromal invasion beyond the capsule in EPC, are considered as diagnostic features of invasive disease.

The most common papillary lesion in the breast is benign intraductal papilloma, also called solitary/central papilloma. However, other entities, despite being rare, attract more attention due to their unique nature and behaviour, particularly EPC and SPC. Invasive papillary carcinoma (IPC) is very rare and poorly defined, making extraction of reliable data on its behaviour a challenging task. The diagnostic work-up of papillary lesions includes a spectrum of diseases with typical benign intraductal papilloma at one end and IPC at the other end of the spectrum. There are the lesions in the middle of the spectrum that comprise one of the most challenging diagnostic entities in breast pathology. These challenges often stem from one or more of the following. (1)

Fig. 1 Encysted/encapsulated papillary carcinoma (EPC) which shows mainly solid growth pattern and appears to lack the thick fibrous capsule mimicking solid papillary carcinoma (SPC). This tumour lacks other features of SPC including neuroendocrine differentiation, mucinous differentiation, nuclear palisading and spindling and it shows typical cystic morphology in other parts of the lesion.

Table 1 Role of myoepithelial cells in the diagnosis of papillary lesions

Papillary lesion	ME cells in papillae (epithelial/fibrous core interface)	ME cells at periphery (tumour/adjacent stroma interface)
Papilloma	Present	Present
Papilloma with atypia/DCIS	Present but absent/reduced in atypical areas	Present
Papillary DCIS	Absent	Present
Encapsulated PC	Absent	Frequently absent (>85%)
Solid PC	Absent	Usually absent (>70%)
Invasive PC	Absent	Absent

DCIS, ductal carcinoma *in situ*; ME, myoepithelial cells; PC, papillary carcinoma.

Overlapping morphological and immunohistochemical features among benign, atypical and malignant papillary lesions. (2) Lack of reliable and reproducible criteria for the diagnosis and classification of certain papillary lesions. This is more commonly experienced with cases featuring low nuclear grade atypia and more rarely in cases featuring diffuse high-grade atypia with or without triple negative phenotype or HER2 positivity.¹⁰ Also, diagnostic features that can be reliably used to distinguish pure (pTis) from invasive (pT) EPC and SPC remain unclear, subjective and difficult to apply to individual tumours. There is a lack of clear criteria to differentiate EPC with partially solid growth pattern or focally lacking fibrous capsule from SPC, or distinguish SPC and EPC showing multinodular growth pattern from papillary DCIS (Fig. 2). Assessment of prognostic and predictive parameters in invasive disease associated with non-invasive PC is also subjective and related to interpretation of vague features defining invasion in these lesions. (3) Papillary lesions are more prone to epithelial displacement, sclerosis with epithelial entrapment and can feature florid epithelial proliferation and prominent adenotic growth pattern resulting in appearances that can mimic invasive carcinomas.¹¹ This can be confounded by focal lack of peripheral ME cells as seen in some cases. Benign papilloma may also show some degree of

Fig. 2 Papillary carcinoma showing overlapping features between papillary ductal carcinoma *in situ* (DCIS) and multinodular encapsulated papillary carcinoma (EPC). Myoepithelial cell immunohistochemical markers may help in this differential diagnosis.

ME hyperplasia or chondromyxoid metaplasia and these should be differentiated from adenomyoepithelioma (Fig. 3) and pleomorphic adenoma, respectively, despite the vague boundaries between these entities. (4) In addition to the difficulty and subjectivity in applying existing diagnostic criteria in the classification of papillary lesions, some pathologists may not concur or be reluctant to use certain established diagnostic features in breast pathology differently in the context of papillary lesions. For instance, designating a malignant lesion lacking peripheral ME at epithelial stromal interface, as seen in most SPC and EPC, as an *in situ* disease is not in line with the commonly used definition of invasion used in breast pathology. The concept of invasion within and beyond the fibrous capsule in EPC is confusing and not evidence based. Similarly, using tumour outlines and pattern of growth to distinguish *in situ* from invasive SPC appears subjective and not evidence based but rather descriptive and based on personal experience and opinion. Furthermore, changing the approach to the diagnosis and categorisation of SPC and EPC over time, with demonstration of loss of ME cells in PC and reported invasive events in different studies, may have resulted in reducing diagnostic concordance among reporting pathologists.⁷ The recommendation of management of PC as *in situ* disease (pTis) despite the probable indolent

Fig. 3 Papillary lesions with prominent myoepithelial proliferation in keeping with adenomyoepithelioma.

invasive biological behaviour and the lack of peripheral ME cells is understandable and justifiable.^{6,12,13} However, what constitutes PC and invasive PC remains based on pathologists' interpretation of multiple features, the majority of which are subjective. This is likely to have management implications, as patients with the same tumours will be managed differently based on whether the pathological diagnosis is *in situ* or invasive disease.

In previous concordance studies of 240 breast lesions included in the UK National Health Service Breast Screening Programme breast pathology interpretive external quality assurance scheme that includes more than 600 pathologists,^{14,15} papillary lesions comprised the most frequent diagnostic misinterpretation; 9 of 13 discordant cases (69%) were papillary. Although the scheme is based on a single representative haematoxylin and eosin (H&E) stained slide from each case, histological review of these cases revealed diagnostic misinterpretation of the morphological findings even when considering the lack of ancillary techniques.¹⁵ The identified diagnostic challenges of PC included not only categorisation as *in situ* or invasive disease (18–27% of pathologists over- or under-diagnosed PC as *in situ* or invasive carcinomas) but also under-recognising PC as benign/atypical lesions. PC and papillary DCIS were diagnosed as benign/atypical lesions by 5–12% of the participants and 4–5% reported them as benign tumours without atypia. Moreover, 28% of the participants under-diagnosed invasive PC as *in situ* disease.¹⁴ Regarding benign papillary lesion, 16–20% of the participants called papilloma with florid epithelial hyperplasia, stromal sclerosis and either mild apocrine atypia or myoepithelial hyperplasia as DCIS. This is likely to represent over-interpretation of the cytonuclear changes observed in more than 3 mm of the lesion but immunohistochemistry (IHC) may help in such cases.¹⁵ Epithelial hyperplasia, sclerosis with entrapped epithelium in benign papilloma was over-diagnosed by 1–6% of participants as invasive carcinoma, but again lack of IHC use may explain this high frequency of over-interpretation.¹⁵ Table 2 shows a summary of the challenges in the diagnosis of papillary lesions with some recommendations on interpretation. As features characteristic of each specific entity have been described in detail elsewhere, this review will focus on the diagnostic challenges and how to improve diagnostic concordance of these lesions.

DIAGNOSTIC CHALLENGES IN BENIGN PAPILLARY LESIONS

Differentiating benign from malignant papillary lesions

In malignant papillary lesions, the papillae are usually more delicate and less fibrotic than those of benign intraductal papilloma. This, together with the fact that malignant lesions show increased nucleocytoplasmic ratio, generally results in a basophilic (blue) appearance on low magnification. Benign lesions often show eosinophilic (pink) appearance which may also be exaggerated by the presence of apocrine metaplasia and contribution by ME cell component. The epithelium in malignant lesions is composed of a single cell population with a uniform appearance compared to the heterogeneous variable appearances of the component cells in benign lesions resulting from the presence of a heterogeneous mixture of epithelial, ME and basal cells.

ME cells are maintained at the epithelial/stromal interface throughout, within the cores and at the periphery of the benign papillary lesions and are absent in the cores of malignant lesions. They are frequently absent at the periphery of EPC and SPC (~80% of cases) and always totally absent in IPC (Table 1).

Florid epithelial proliferation that may partially or completely obliterate the spaces between papillae can be seen in both benign and malignant entities; however, malignant lesions typically show polarisation of the proliferating neoplastic cells with a flat, solid or cribriform architecture.

Spindling and peripheral palisading of the proliferating cells, intracellular mucin secretion and neuroendocrine differentiation are typically seen in malignant lesions, usually of the solid papillary type. Spindling of cells in SPC needs to be differentiated from streaming of cells seen in epithelial hyperplasia in benign papilloma in view of the overall appearance of the lesion and use of IHC in difficult cases.

Other important findings that may help are the presence of bland-looking apocrine metaplasia in benign and increased mitotic figures in malignant papillary lesions. Surrounding breast tissue may also help, as papilloma may be associated with fibrocystic changes or other benign lesions, while PC may be associated with DCIS.

The last and very helpful tool to differentiate benign from malignant papillary lesions is IHC using a panel of markers to assess the presence of ME cells, tumour cell clonality and other markers such as those used for detecting neuroendocrine and mucinous differentiation that are typically absent in benign papillary lesions (see below and Table 3).

Atypia in papilloma

Atypia in a papilloma is often of low nuclear grade. High nuclear grade atypia is uncommon and when it is present the lesion is diagnosed as high grade DCIS involving a papilloma, regardless of the extent of atypia. Diagnosis of intermediate grade atypia in papilloma is challenging and subjective. A pragmatic approach is to use IHC. The presence of hyperplasia of usual type (HUT) in benign papilloma may also raise the possibility of intermediate grade DCIS, especially if there are occasional mitotic figures and aberrant degree of pleomorphism resulting from the presence of different cell types and reactive changes. Moreover, high molecular weight/basal cytokeratin (CK) expression can occasionally be seen in DCIS, making differential diagnosis with HUT challenging. However, basal CK expression is typically seen in high nuclear grade 'basal-type' DCIS that show definite high grade cytological atypia on H&E, unlike HUT. Architecture and oestrogen receptor (ER) IHC may also help in this context.

Diagnosis of low nuclear grade atypia in a papilloma relies on the same criteria for diagnosis of ADH elsewhere in the breast.^{1,13} Generally, the areas of atypia exhibit focal solid or cribriform epithelial expansion with proliferation of small, monotonous and evenly spaced epithelial cells. On IHC these areas lack staining of basal CK (CK5/6, CK14 and CK17) and show diffuse strong positive nuclear ER staining. ME cells are reduced or absent in these areas. If this area of atypia is small (<3 mm) in size, the diagnosis of papilloma involved by ADH is warranted, while if this focus is large (≥3 mm) the lesion is diagnosed as DCIS involving a papilloma.¹ IHC may help in determining the size of atypia in challenging and

Table 2 Diagnostic challenges in papillary lesions of the breast

Diagnostic challenges		Recommendations
A: Benign/atypical papillary lesions		
1	Identification of low nuclear grade atypia in a benign papillary lesion	Same criteria for differentiating hyperplasia of usual type from ADH/low grade DCIS
2	Differentiating ADH from DCIS in benign papillary lesion	3 mm cut-off; if in doubt about size use IHC to delineate area of atypia
3	Diagnosis of high grade DCIS in a papilloma	High nuclear grade features of any extent (no size cut-off). Surrounding tissue may show DCIS. IHC is of limited value in identification of high grade DCIS
4	Exclusion of invasion in benign papilloma showing florid epithelial hyperplasia associated with sclerosis and entrapped epithelium/glands typically seen at the edge of sclerosed papilloma. Some cases even show focal loss or attenuation of myoepithelial cells. Also in cases featuring prominent core biopsy site related changes with fibrosis and entrapped epithelium lacking ME cells at the edge of a papilloma	IHC indicates the hyperplastic nature of the proliferating epithelium with preservation of ME cells at epithelial stromal interface at least focally. Lack of DCIS or conventional type invasive carcinoma in surrounding tissue. Haemosiderin and fat necrosis seen at core biopsy site support epithelial displacement rather than invasion
5	Differentiating small incidental papillary lesion in core biopsy (B2) from true papilloma (B3)	Benign papillary lesion on core biopsy is B3. B2 diagnosis can be used if there is a tiny incidental papilloma that is not representing the mammographic abnormality and is typically part of a fibrocystic change
6	Diagnosis of papillary lesion with low grade atypia on core biopsy	Based on extent of low grade atypia (B3 or B5a; with 3 mm cut-off); IHC is very helpful
7	Identification of lobular neoplasia in benign papillary lesion	Discohesive growth pattern, solid proliferation lacking cribriform architecture; use E-cadherin IHC
8	Differentiating single papilloma from multiple papillomas	Presentation, location, number of involved ducts; less clinical significance as long as atypia is excluded
9	Diagnosis of papilloma showing cytonuclear changes that mimic columnar cell changes/flat epithelial atypia following application of IHC	IHC has to be interpreted with morphology; no complex architecture present
10	Differential diagnosis of papilloma with myoepithelial hyperplasia from adenomyoepithelioma	Focal ME cell proliferation can be seen in papilloma; in adenomyoepithelioma, ME component is predominant with proliferating clusters of cells not just a layer at the epithelial/stromal interface
11	Differential diagnosis of papilloma with metaplastic changes from pleomorphic adenoma, and mucoepidermoid carcinoma	Focal metaplastic changes can be seen in papilloma, but metaplastic component is predominant in PA and mucoepidermoid carcinoma; the latter shows specific genetic abnormality with t(11; 19) (q21; p13) translocation creating MECT1 and MAML2 fusion gene
B: Malignant papillary lesions		
12	Categorisation of some SPC into <i>in situ</i> and invasive disease (different scenarios)	See text
13	Identification of invasion in encapsulated/encysted PC and differential diagnosis from microinvasion or core biopsy site changes and the definition of invasion within and outside the capsule	Papillary lesions in general and PC in particular can show changes mimicking core site related changes. Microinvasion within the capsule is of limited significance but outside capsule is considered as conventional type invasion. Also see text
14	Determination of invasive tumour size in PC with features of invasion	Grade, size, receptors and type should be assessed on the conventional type invasive carcinoma while PC size is added to whole tumour size akin to DCIS
15	Differentiating SPC from EPC	SPC show 6 features that can be used to differentiate from EPC: predominant solid growth pattern with rudimentary core; neuroendocrine differentiation in around 70% of cases; nuclear palisading; intracellular mucinous differentiation, streaming or spindling of the cells; lack of well-developed fibrous capsule. SPC are also more frequently multinodular, show low nuclear grade features and are more frequently associated with invasive carcinoma, particularly mucinous carcinoma (see Table 4)
16	Differentiating papillary DCIS from multinodular PC (EPC)	Presence of peripheral ME cells and number of involved ducts
17	Differentiating papilloma involved by DCIS from PC	See text
18	Differentiating PC from pure IPC	See text
19	Diagnosis of PC on a core biopsy (B5a or B5b)	The current approach is to call PC on core biopsy as B5a akin to DCIS unless definite evidence of stromal invasion is seen. If imaging suggestive of invasion, MDT discussion is recommended for sentinel node sampling
20	Diagnosis of PC with high histological grade features	See text ¹⁰
21	Grading of PC	We use Nottingham grading system for invasive PC and nuclear grading system for <i>in situ</i> PC akin to DCIS
C: Other challenges		
22	Epithelial displacement in papillary lesions	See text
23	Diagnosis of invasion in areas of sclerosis and epithelial entrapment	Index lesion is benign. IHC for ME cell markers and basal CKs may help. Invasive-looking structures are located within fibrous tissue at periphery of lesion with no fat infiltration or infiltration of background tissue away from the index lesion
24	Differential diagnosis of papilloma from skin appendage tumours with papillary configuration such as hidradenoma due to lack of ME cells	In these cases lack of ME together with the papillary architecture may be interpreted as malignant papillary lesion. The superficial location, diffuse strong staining of basal CKs and p63 help in diagnosis of a skin lesion
25	Basal CKs and ME cell staining challenges, i.e., apocrine	Apocrine differentiation may be associated with reduced/loss of ME cells. Cytological features and architecture of the proliferating apocrine cells should differentiate benign from malignant lesions. Absence of ME cells in papillary lesion featuring apocrine morphology should not be used alone to indicate malignancy ^{48,50}

(continued on next page)

Table 2 (continued)

	Diagnostic challenges	Recommendations
26	Metastatic papillary carcinomas, i.e., thyroid	History of thyroid carcinoma, IHC including TTF1, ER, GATA3, and thyroglobin would help ^{41–46}
27	Solid lobular carcinoma may mimic EPC with well-defined margin, focal pseudocapsule and central fibrovascular cores	Cytological features of lobular cells and E-cadherin staining can differentiate both entities ⁵³
28	Use and interpretation of IHC in the diagnosis of papillary lesions	See text
29	Differentiation between SPC and NE carcinoma	NE markers in the context of SPC are diagnostic and not of prognostic value. Positivity of NE markers can be used to support the diagnosis of SPC over EPC or HUT but the distinction between <i>in situ</i> and invasive forms of SPC is based on the absence of ME cells and the overall architecture. Diffuse strong ER positivity is not a typical feature of carcinoid tumour
30	Differentiating PC from secretory breast carcinoma with prominent papillary architecture	Secretory carcinoma typically affects young patients, and secretory activity is often identified. IHC with ER and S100 would help in addition to demonstration of ETV6-NTRK3 fusion gene in secretory carcinoma but not in PC

ADH, atypical ductal hyperplasia; CK, cytokeratin; DCIS, ductal carcinoma *in situ*; EPC, encapsulated papillary carcinoma; IHC, immunohistochemistry; IPC, invasive papillary carcinoma; ME, myoepithelial; NE, neuroendocrine; PC, papillary carcinoma; SPC, solid papillary carcinoma.

borderline cases. However, as stated in the World Health Organization (WHO) classification,¹ the size criteria are not based on evidence and a pragmatic approach should be adopted when dealing with borderline avoiding over-diagnosis. The term atypical papilloma is discouraged. Sometimes the papilloma is completely involved by the atypical cells making differential diagnosis of papilloma overrun by DCIS and papillary DCIS or PC challenging. The clue would be demonstration of residual structure of the benign papillary lesion, which is often IHC evidence of ME cells within the cores or residual HUT. Also papillary DCIS is typically multifocal, whereas papilloma with DCIS is most often a large solitary lesion. Cases lacking evidence of underlying residual benign papillary lesions are termed papillary carcinoma (PC). Sometimes the atypical cells show a moderate degree of pleomorphism and mitotic figures and in such cases a diagnosis of intermediate grade DCIS can be made using the same criteria for grading DCIS elsewhere.

In our routine diagnostic work, homogeneous ER staining has also been encountered in papillomas, notably when there is a columnar cell-type change seen in the lining epithelium with diffuse strong nuclear staining of ER and lack of basal CK. Strong and diffuse ER staining has also been noted in 5% (1/20) of benign papillary lesions in a published cohort.¹⁶ Occasionally papilloma may be involved by lobular neoplasia. In such cases, the cellular monotony, dyshesion, pagetoid pattern of growth and E-cadherin staining can provide a clue to its diagnosis.

The presence of atypia in the form of ADH, flat epithelial atypia, lobular neoplasia or DCIS in papilloma is expected to have a relative risk of invasive malignancy similar to that of atypia elsewhere in the breast when they occur as pure forms or associated with other lesions such as fibrocystic changes. It has been reported that the relative risk of developing breast cancer in patients with papillomas involved by atypia is 5–7.5-fold greater than in patients with papillomas without atypia.^{17,18} Currently in the UK the recommendation of management of ADH involving a papilloma is different from pure ADH in which surgical excision is recommended to assess the extent of atypia.¹⁹ On surgical specimens, assessment of the margin of excision in case of atypia involving papilloma may be challenging. It is our approach to pay attention to the surrounding breast tissue and the completeness of excision of the papilloma in such cases, without the need for

a wide margin. There is some evidence to suggest that the risk of recurrence is related to the atypia in the surrounding tissue rather than to atypia within a papilloma, provided that the papillary lesion containing atypia is excised.^{1,18} There is no evidence that papilloma involved by DCIS or papillary DCIS has different behaviour and therefore differentiating both lesions may have limited clinical significance. However, as PC may have a low risk of invasive behaviour, differentiating papilloma involved by DCIS from PC may have implications regarding the clinical behaviour. Fortunately both lesions currently have the same treatment strategy.

Mimics of invasion in papillary lesions

Although in benign papilloma focal fibrosis and sclerosis with entrapped irregular epithelial elements are not uncommon, some cases show marked changes mimicking invasive tumour. However, the cytological features and architecture of the entrapped cells in these areas, the benign nature of the index papilloma and the demonstration of peripheral ME cells using IHC in difficult cases can confirm their benign non-invasive nature. Helpful clues to entrapped epithelium also include lack of angulated glandular structure and the smooth contour of the epithelial clusters that tend to flow in the direction of the fibroblasts and bundles of collagen. These areas of fibrosis with entrapped epithelium can be localised, suggesting previous biopsy sites. However, we often see such changes in multiple foci around the papillary lesion circumferentially, which may reflect the cystic nature of these lesions that may undergo repeated minor rupture, with associated tissue reaction, due to increase intraluminal pressure following distal duct obstruction. Although differentiation of this pseudo-invasion pattern from frank stromal invasion in benign papilloma is typically straightforward, such differentiation in PC is problematic. Many PCs are bounded by zones of fibrosis, chronic inflammation and recent or resolved haemorrhage. Papillary or tubular structures are routinely found within these areas, parallel to the layer of reactive stroma and these do not constitute invasion but rather entrapped epithelium (see below).

Epithelial displacement in papillary lesions

Epithelium displaced by a needle core or aspiration biopsy is more frequent in papillary lesions including benign and

Table 3 Differentiation between benign and malignant papillary lesions

Variables	Papilloma	Papillary carcinoma
Age	30–55 years	55–75 years
Appearance	Eosinophilic (pink)	Basophilic (blue)
Fibrovascular core	Usually broad and easily identified on low power view; may be sclerotic	Usually fine and less fibrotic; best detected on high power view or even with the use of IHC for ME markers
Cell types	Biphasic (epithelial and ME cells); in hyperplastic areas there is proliferation of epithelial and basal cells	Single cell type (epithelial/luminal type) clonal/neoplastic proliferation
Nuclei	Normochromatic and variable in size and shape	Hyperchromatic and usually uniform with increased nuclear/cytoplasmic ratio; high grade features are not features of typical PC
Cell orientation	Haphazard; may show HUT	Orderly, solid or cribriform; may show mucinous secretion, spindle, columnar or transitional epithelium
Mitosis	Infrequent/absent; occasional mitosis may be seen in areas featuring florid hyperplasia	More frequent (>1/10 HPF); abnormal mitotic figures are rarely seen
Apocrine metaplasia	Frequent (~36%), benign	Absent (<15%); if present it shows cytological and architectural atypia
Secondary changes	Focal/minimal degree of squamous metaplasia, myoepithelial hyperplasia, chondromyxoid and mucinous metaplasia and extensive sclerosis with entrapped glands mimicking invasion may be seen	Uncommon but SPC frequently show mucinous and neuroendocrine changes; intracystic haemorrhage may be seen
IHC	Heterogeneous/mosaic expression of basal CKs and ER; no expression of NE markers	Negative expression of basal CKs; diffuse strong nuclear positivity of ER; NE marker expression can be seen (60–70%) in SPC
Adjacent ducts	Benign changes	DCIS may be seen in the surrounding tissue

CK, cytokeratin; DCIS, ductal carcinoma *in situ*; ER, oestrogen receptor; HUT, hyperplasia of usual type; ME, myoepithelial; NE, neuroendocrine; PC, papillary carcinoma; SPC, solid papillary carcinoma.

malignant entities because of their inherent friability. The epithelium can be dislodged and displaced into the surrounding stroma, often in the needle tract, and even into adjacent lymphatic channels mimicking lymphovascular invasion, or transported to axillary lymph nodes.¹¹ It is important to be aware of the possibility of displacement after biopsy procedures to distinguish displaced epithelium from true stromal or lymphovascular invasion. The presence of prior biopsy site changes, degenerative changes in the 'invasive' cell clusters, and absence of reactive, altered stroma surrounding the fragments of epithelium are clues indicating epithelial displacement. The nature of the displaced epithelium is best determined based on the nature of the underlying papillary lesion. In benign papillary lesions, lack of peripheral ME cells around the displaced epithelial clusters should not be used as a criterion to define malignancy but rather mechanical effect during the process of displacement. Moreover, the presence of displaced epithelial clusters at the surgical margin in malignant papillary lesions should be disregarded during assessment of completeness of excision or tumour size measurement, despite the fact that they are likely to be malignant.

DIAGNOSTIC CHALLENGES IN PAPILLARY CARCINOMAS

General considerations

PC account for 0.5–1% of breast cancers.^{2,3,5–7,10,20–25} They can be either localised and form an expansile mass corresponding to EPC and SPC or diffuse within TDLUs and correspond to papillary DCIS.^{2,3,5,26–28} Compared to EPC, SPC is typically solid, characterised by mucin production, neuroendocrine features and multinodular architecture^{6,12,28,29} while papillary DCIS is typically surrounded by a peripheral layer of ME cells.^{5,7,13,27} The term EPC has been

introduced to define PCs that are typically circumscribed and encapsulated (separated from surrounding mammary stroma by a fibrous capsule) and often lacking ME cells at their periphery.^{6,7} Although we and others have included SPC in the term EPC,^{7,28,29} the current view is to consider them as separate entities but with acknowledgement that some cases show overlapping features and are difficult to distinguish from each other.⁶

PC can be present as an isolated lesion or associated with conventional non-papillary *in situ* or invasive carcinoma. The term PC is used in the literature to describe a heterogeneous group of malignant neoplasms including non-invasive (*in situ*) and invasive carcinomas and its classification remains extremely varied.^{2,3,6,9,12,13,20,27,30,31} Although categorisation of papillary DCIS and IPC as *in situ* and invasive disease, respectively, is easy and straightforward, categorisation of EPC and SPC into an *in situ* (non-invasive) or invasive disease created a great deal of debate and controversy, as detailed above, due to the mismatch between histological features and clinical behaviour.^{6,7,12,13,20,23,24,32–38}

However, the current opinion is to stage these tumours as *in situ* disease (pTis),^{6,12} a view which is supported by the very low incidence of invasive behaviour that is far lower than conventional forms of invasive breast carcinoma. However, this results in confusion with categorisation and management of PC among reporting pathologists.¹⁴ Discordance of diagnosis of tumours showing the same histological features will result in a subsequent variation of management of the same tumours diagnosed at different institutions¹⁴ regardless of the recommendation for management. A proportion of PCs will potentially be diagnosed by certain pathologists as invasive and managed similar to other often aggressive conventional-type invasive carcinomas, while other pathologists will diagnose them as PC (pTis) and they will be subsequently managed as DCIS. This concern is also

supported by the varied proportion of cases termed as IPC in the published literature (from 13%^{26,39} to 59%⁴⁰ of PC classified as invasive). It is logical to be aware of the existing but very low risk of invasive behaviour in PC and we have proposed a new terminology for these lesions as malignant tumours with limited metastatic potential. This reflects the presence of a degree of uncertainty regarding their clinical behaviour³² and encourages pathologists to accept their categorisation as *in situ*, despite the histological appearances, and clinicians to accept that the possibility of invasive behaviour cannot be entirely excluded.

Diagnosis of minimally invasive PC can be difficult. Frank invasion is recognised by the presence of neoplastic cells with infiltrative appearances beyond the zone of reactive stroma into mammary parenchyma and fat. Invasive areas, in general, do not display papillary features (frond-forming), but rather exhibit the morphology of a conventional invasive ductal NST or other types such as mucinous and invasive cribriform carcinoma. Cytological appearances are varied and nuclear pleomorphism and increased numbers of mitoses may be seen. Mucin secretion is frequently seen in PC, particularly the solid variant, and in such cases it should be distinguished from mucinous carcinoma. In most cases micropapillary or cribriform DCIS is present in adjacent ducts.

Intraductal papillary carcinoma (papillary DCIS)

Although intraductal PC is the term endorsed by the WHO working group and is used to describe this lesion in the relevant chapter of the 4th edition of WHO classification,¹³ here we refer to it by the most frequent term that we use in routine practice (papillary DCIS) to avoid confusion with other PC. Papillary DCIS is basically a variant of DCIS and therefore requires similar management. It is typically peripheral in location, may appear multifocal, and usually co-exists with other variants of DCIS, particularly cribriform DCIS. Therefore, it is important to distinguish papillary DCIS from PC with prominent multinodular growth pattern. Papillary DCIS show smooth contours with well-defined ductal profiles surrounded by an intact layer of ME cells at the periphery. PC with a multinodular growth pattern typically lack a peripheral ME cell layer and usually have an index larger expansile circumscribed lesion. PC with exaggerated multinodular growth pattern and lacking ME cells should be differentiated from IPC. In such cases IHC for ME cell markers is of great importance in the differential diagnosis. In papillary DCIS the neoplastic cells often appear bland and are categorised as low or intermediate grade; however, high-grade papillary DCIS do occur, albeit with lower frequency. Apocrine differentiation may be present and prominent leading to classification as apocrine papillary DCIS, but this distinction does not have clinical significance.

It should also be noted that although most papillary DCIS, EPC and SPC have a single, uniform cell population, some feature a dimorphic cell population, in which the second population exists and consists of cells with abundant, pale cytoplasm that are most often in a basal location; the so called 'globoid cells'. These cells should not be mistaken for ME cells and can be distinguished from them with epithelial and ME IHC markers. Globoid cells are positive for luminal low molecular weight CKs and GCDPF-15 and negative for ME markers.

Encapsulated papillary carcinoma (EPC)

EPC was traditionally termed 'encysted' or 'intracystic' papillary carcinoma to reflect its cystic circumscribed nature. Presentation of EPC may be indistinguishable from that of solitary papilloma, apart from the tendency of EPC to affect elderly patients and being larger in size.^{6,7} EPC is often solitary but occasionally multiple nodules are present with at least the main mass showing a thick fibrous capsule. Neoplastic cells are often monomorphic and bland looking and are typically graded as low or intermediate grade. They are positive for oestrogen and progesterone receptors and negative for HER2. High grade lesions are extremely rare and should be classified as invasive disease.¹⁰ These high grade tumours often show triple negative or HER2 phenotype. In addition, it is not uncommon to find entrapped neoplastic epithelial cells within the fibrous capsule, a feature that may be interpreted as part of the nature of PC/microinvasion or frank invasion in PC. However, this phenomenon appears to have no or insignificant clinical impact⁷ and we follow the old concept of considering invasion in EPC when it is outside the fibrous capsule. Some authors even tried to define stromal invasion in EPC by the presence of malignant papillary clusters 10 mm or more beyond the capsule,³⁶ which may emphasise our old perception of the biological value of the capsule in EPC. Typical EPC may also be associated with focal conventional type non-papillary invasive carcinoma such as ductal no special type (NST) or mucinous carcinoma. These can range from small/microinvasive to larger invasive areas. Assessment of prognostic and predictive factors should be limited to these frank invasive foci while EPC is considered only for assessment of whole tumour size akin to DCIS.

Another challenge in the diagnosis of EPC, but more problematic in SPC, is occurrence as multiple nodules of variable size and irregular outlines. This creates the problem of trying to differentiate typical EPC and SPC from the invasive forms of PC. In an attempt to differentiate *in situ* from invasive SPC and EPC, some authors defined invasion as nests showing papillary architecture (blunt invasion) and displaying a pattern inconsistent with that of branching ducts or terminal duct lobular units located within non-specialised stroma.^{2,20,35} In fact this diagnostic challenge of using the concept of blunt stromal invasion and multi-nodularity with description of the relationship between nodules and jigsaw pattern of growth to distinguish *in situ* from invasive PC is mainly observed in SPC. Invasion in EPC is frequently non-papillary such as ductal NST or lobular carcinoma seen beyond the capsule which is easy to identify. The difficulty often arises in rare cases of EPC in which there is deficiency of the peripheral fibrous capsule with irregular outlines and stromal invasion-like epithelial growth seen at one or multiple foci typically lacking ME cells. We have also seen a few cases featuring multiple PC-like nodules lacking peripheral fibrous capsules and ME cells and showing irregular outlines. It is our approach to consider these cases as low grade invasive PC with no requirement for adjuvant chemotherapy. Another criterion that can be used for the diagnosis of IPC in PC is the presence of a component of invasive micropapillary carcinoma with otherwise typical PC. Invasive micropapillary carcinomas are typically associated with worse prognosis and we believe that presence of such component should render the diagnosis of invasion more likely.

Solid papillary carcinoma (*in situ* and invasive SPC)

SPC is a distinctive form of PC characterised by round, well-defined nodules composed of low-grade ductal cells separated by fibrovascular cores. Some cases of SPC have been reported in literature as spindle cell DCIS, neuroendocrine DCIS and endocrine DCIS.¹² The most recent WHO classification of these tumours emphasises the need to distinguish pure *in situ* forms from those with associated or pure invasive disease. SPC are positive for oestrogen and progesterone receptors and negative for HER2. Proliferation index is typically low. However, we have seen occasional cases featuring typical SPC appearances with focal high grade areas showing increased mitotic figures. The significance of this is uncertain as long as no definite invasive carcinoma is identified. The majority of SPC lack peripheral ME cells and differentiating non-invasive from invasive disease is considered a challenge, particularly in the multinodular forms with some irregular outlines of the nest. Rare SPC with an intact peripheral ME cell layer are a variant of DCIS. Some SPC show peripheral fibrous tissue capsule akin to EPC but this is typically incomplete and not well-developed. The differential diagnosis of SPC ranges from benign to malignant lesions including florid HUT, EPC, and ordinary low nuclear grade solid DCIS. Florid HUT does not have fibrovascular cores, palisading of cells, neuroendocrine differentiation or mucin production. IHC is very helpful in difficult cases as discussed above. Table 4 summarises the main distinguishing features between SPC and EPC.

Compared to EPC, SPC is more frequently associated with co-existing invasive carcinoma and an association between large tumour size and the presence of invasion in SPC has been reported.⁴⁰ Invasion in SPC can be classified into two types. (1) SPC associated with conventional type invasive carcinoma. The invasive component may have a pure or mixed mucinous, neuroendocrine-like, invasive ductal NST, or rarely lobular or tubular type. In general, the invasive carcinoma component is low to intermediate grade and often shows cytological features similar to the adjacent SPC. (2) Tumours showing predominant SPC pattern but with features supporting stromal infiltration. SPC is more often multinodular with multiple rounded duct-like structures. The current opinion is to consider SPC as invasive disease if the cell nests show geographic jigsaw pattern of growth with more ragged and irregular margins. It is our experience that most of these cases show wide-spread invasive pattern with at least focally high grade nuclear features and mitotic figures and they may show vascular invasion. SPC frequently show intracellular mucinous differentiation which when present raises the possibility of SPC rather than EPC. Focal extracellular mucinous differentiation can be seen but attention should be paid to differentiate such areas from invasive mucinous carcinoma (Fig. 4). Prominent extracellular mucin with malignant cells floating in pools of mucin that are typically seen at the periphery of some SPC with focal extension into stroma should qualify the diagnosis of mucinous carcinoma arising in a background of SPC. A pragmatic approach should be taken to assess prognostic and predictive factors in such tumours. In the absence of frank invasion, we render a diagnosis of PC and include an explanatory note stating that although these cases should be managed as *in situ* disease there is a degree of uncertainty regarding their behaviour.^{7,32}

Fig. 4 A case of solid papillary carcinoma (SPC) with prominent extracellular mucin secretion suspicious of mucinous carcinoma. This case shows multiple areas of extracellular mucin section at the periphery of SPC masses with floating of malignant cells in mucin lakes consistent with mucinous carcinoma arising in SPC.

In the absence of co-existent conventional invasive carcinoma, SPCs have a favourable outcome. In cases associated with invasive carcinoma, the prognosis will depend upon the invasive component of the tumour. The behaviour of pure invasive SPC as defined above without conventional type carcinoma is unknown but it is prudent to report tumours showing such features as invasive disease (invasive SPC; Fig. 5) in routine practice and sufficient data on their outcome may emerge in the future. Complete excision of the lesion is the treatment of choice in PC. As these cases are staged as pTis disease, sentinel lymph node may not be indicated. However, the high frequency of co-existent invasive conventional type carcinoma, and the possibility of changing the diagnosis to invasive SPC on excision specimen, makes recommendation for sentinel node biopsy advisable or subject to further discussion. Also the majority of these tumours are oestrogen receptor strongly positive, making those patients candidates for hormone therapy, especially when surgery is not possible.⁷

Invasive papillary carcinoma (IPC)

The term IPC is reserved for invasive carcinomas exhibiting an exclusively papillary morphology in >90% of the invasive tumour and should be distinguished from the other malignant papillary lesions described previously. Invasive non-papillary carcinoma associated with EPC or SPC should not be classified as IPC but categorised according to the individual invasive component. Defined as such, IPC is extremely rare.⁹ The microscopic features of IPC may mimic papillary DCIS but with frank invasive growth pattern, comprising mildly dilated ducts, glands and microcysts containing papillary cores, and lack of ME cells. The size of the invasive structures may vary but are typically small with no peripheral fibrous capsule/pseudocapsule unlike EPC or SPC. The stroma may show desmoplastic response. True IPC should also be differentiated from invasive micropapillary carcinoma, which is a clinically and pathologically separate entity.

Fig. 5 A case of solid papillary carcinoma (SPC) that progressed to invasive SPC. (A) Central region of the tumour featuring residual SPC with some features of invasion. (B) Peripheral region of the tumour with frank invasive morphology but with similar cytology to the central tumour parts together with occasional fibrovascular cores of the residual papillary structures.

However, some tumours may show features overlapping with both tumour types (Fig. 6). IPC should also be differentiated from metastatic non-mammary carcinomas with papillary architecture such as papillary thyroid carcinoma. The prognosis of IPC appears to be related to tumour grade and stage.⁹ The good prognosis of IPC reported in the literature is mainly derived from cases of EPC and SPC associated with invasion⁸ and cannot be reliably used to reflect the behaviour of true IPC as defined above.

Fig. 6 (A) A case of pure invasive micropapillary carcinoma as compared to (B) a case of invasive carcinoma with papillary and invasive micropapillary features.

Risk of recurrence of papillary carcinoma

Papillary DCIS, EPC and SPC have a risk of local recurrence and very low risk of obscure invasion, slightly higher than occurs with other types of DCIS, particularly the EPC and SPC variants. In a previous study which included 917 EPC, it was reported that the prognosis is excellent even if PC is associated with invasion;⁸ however, complete local excision is important and sentinel lymph node biopsy may be a prudent way to evaluate axillary involvement in cases featuring or suspicious of invasion. There is scanty data on the outcome of IPC but it may be prudent to manage these tumours akin other forms invasive breast carcinomas of similar grade, stage and receptor status.

Rare variants of papillary carcinomas

Papillary lesions may show a wide range of differentiation and metaplastic changes. PC having histological features similar to those of the tall cell variant papillary thyroid carcinoma have been described.^{41–43} These tumours are typically composed of columnar cells arranged in nests, papillae, and follicle-like structures with reverse of polarity. In addition, nuclear grooves are typically seen and ground glass appearing nuclei, nuclear pseudo-inclusions and psammoma bodies may be present.^{41,42} These rare tumours are reported to show hormone receptor negativity, high frequency of associated invasive carcinoma and lack immunoprofile of thyroid papillary carcinoma.⁴⁴ However, to reflect the uncertainty regarding the nature and existence of this as a distinct entity, it has been reported that the architectural and cytological features characteristic of these tumours are also seen in a proportion of intraductal and EPC and are not limited to the described entity of PC.⁴⁵ Some authors have suggested the term 'tall cell variant of papillary breast carcinoma' instead of 'breast tumour resembling the tall cell variant of papillary thyroid carcinoma'⁴⁶ whilst others have called them 'solid papillary carcinoma with reverse polarity (SPCRP)'⁴⁷ and reported a specific type of mutation involving *IDH2* and *PIK3CA* genes. The description of these tumours as a distinct entity different from EPC and SPC may add more confusion for reporting pathologists and clinicians alike. Whether they are variants of SPC, or indeed EPC with a prominent degree of differentiation towards papillary thyroid carcinoma features, and the role of *IDH2* gene mutation in these tumours, remain to be defined.

Table 4 Differentiation between encapsulated (EPC) and solid (SPC) papillary carcinomas

Variables	EPC	SPC
Anatomy	Usually solitary and central	Usually central and more often multinodular but may involve peripheral areas
Appearances	Typically cystic but may show solid areas focally	Typically solid
Peripheral capsule	Usually well-developed and continuous	Usually not well-developed and focal
Papillary cores	Smaller than in papilloma but obvious	Rudimentary, inconspicuous
Cells	Similar to those of DCIS but may be columnar	Frequently show neuroendocrine and mucinous differentiation and may show spindle cell morphology
Nuclear palisading	Absent or only focal	Focal or diffuse and obvious
Associated invasion	Less frequent; when present usually of NST but other types may occur	More frequent; when present usually mucinous but may be NST or invasive solid papillary type

DCIS, ductal carcinoma *in situ*; NST, no special type.

Rare cases of EPC with pure apocrine morphology have also been reported. These cases tend to be cystic and show variable degrees of cytological atypia and mitotic activity and are reported to have indolent behaviour.^{48–50} Some other rare lesions which may show papillary architecture and should be considered during diagnosis of papillary lesions include clear cell carcinoma,⁵¹ secretory carcinoma, and metastatic carcinomas with papillary architecture such as papillary thyroid carcinoma. We have seen a case of metastatic medullary carcinoma of the thyroid to the breast that presented as a solitary metastasis. Morphology revealed papillary architecture but IHC confirmed the diagnosis of medullary thyroid carcinoma. Hidradenoma of the skin can also show papillary configuration and may be mistaken for papilloma or PC on core biopsy due to lack of expression of ME myoid markers. However, these are typically ER negative and show strong expression of basal CKs and p63 in the lesional cells.

MYOEPIHELIAL (ME) CELLS IN PAPILLARY LESIONS

The lack of ME cells in some papillary lesions of the breast remains enigmatic. ME cells are absent within the cores of papillary DCIS and throughout in the majority of EPC and SPC, despite the indolent behaviour of these lesions that suggests an *in situ* nature, at least in a large proportion of cases. Therefore, the presence of a peripheral layer of ME cells in PC confirms its *in situ* nature while their absence does not confer unequivocal evidence of invasion in this context unless associated with other morphological features of frank stromal invasion. It has also been reported that benign apocrine papillary lesions may lack ME cells.⁵⁰ In our practice we have seen papilloma featuring fibrosis with entrapped areas of florid HUT lacking peripheral ME cells at the epithelial stromal interface, particularly at what appear to be invasion fronts. These areas typically show strong staining of both luminal and basal CKs with heterogeneous ER expression mimicking infiltrating epitheliosis of the breast⁵² and these do not change the diagnosis of benign papilloma. The use of ME cells in the diagnosis of papillary lesions is highlighted in Table 1.

IMMUNOHISTOCHEMISTRY OF PAPILLARY LESIONS

The distinction of the different categories of papillary lesions including the distinction between benign and malignant

entities based on H&E morphology can be challenging and IHC has to be used generously in papillary lesions. The most important markers used in papillary lesions are those for ME cells, basement membrane, clonality including oestrogen receptor and basal CKs such as CK14 and CK5/6, and neuroendocrine differentiation. ME markers including p63, myoid markers such as smooth muscle actin (SMA) and smooth muscle myosin heavy chain (SMM), CD10, calponin and basal CKs can be used to differentiate between benign and malignant papillary lesions and between different types of malignant papillary lesions (Tables 1–4). We use a panel of markers to avoid possible false negative results from a single marker.

PAPILLARY CARCINOMA IN MALES

Several studies have reported a greater incidence of PC in males among the various histological tumour subtypes in the breast.⁸ This is mainly related to EPC and SPC with or without associated stromal invasive disease. These studies suggested a two-fold increase in the incidence of invasive PC in males and that IPC is the most frequent rare histological type encountered in males.

CONCLUSION

Papillary lesions of the breast are diagnostically challenging entities with overlapping features and lack of objective diagnostic criteria that can distinguish *in situ* from invasive lesions. The spectrum of these lesions is wide, ranging from benign to invasive carcinomas and their differential diagnoses remain difficult. Awareness of such differential diagnosis and adoption of the published guidelines together with a pragmatic approach, generous use of IHC and discussion with colleagues are likely to improve consistency of diagnosis of these lesions. IHC is extremely useful in the diagnosis of papillary lesions and attention should also be paid to the choice of biomarkers and the interpretation of the results.

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