The road towards conquering DCIS overtreatment

Groen, E.J.

Intraductal papillary carcinoma

Emma Josephine, Groen and Jelle, Wesseling

In: Sapino A, Kulka J, eds. Breast Pathology. Encyclopedia of Pathology. Cham: Springer; 2020:175-180

Synonyms

Noninvasive papillary carcinoma; Papillary ductal carcinoma in situ

Definition

In literature, an unambiguous definition and uniform criteria of intraductal papillary carcinoma is lacking. Often, it is described as a luminal epithelial neoplastic proliferation of the breast confined to the mammary ducts and lobules (also known as ductal carcinoma in situ, DCIS), characterized by a papillary growth pattern. It is considered a potential precursor lesion for breast cancer. Whether these lesions represent de novo malignant papillary epithelial proliferations or malignant epithelial populations transforming and replacing benign papillomas remains unclear.

Clinical features

As intraductal papillary carcinoma is a morphological subtype of DCIS, the following features are derived from literature based on DCIS in general, combined with data specifically focusing on intraductal papillary carcinoma (also known as papillary DCIS).

- **Incidence**
  The incidence of DCIS has dramatically increased since the introduction of population-based breast cancer screening. Nowadays, approximately 20-25% of all breast neoplastic lesions are DCIS. A pure or predominant papillary growth pattern is however rare.
- **Age**
  The reported age range of the patients with malignant papillary lesions in general is 27-89 years with a mean age of 60 (Tse 2005).
- **Sex**
  Predominantly in women.
- **Site**
  The vast majority is asymptomatic and is detected by screening mammography. Symptoms such as nipple discharge, Paget's disease of the nipple, or a palpable mass sometimes occur. There is no preferential site for intraductal papillary carcinoma.

- **Treatment**

  Treatment is similar to DCIS in general. Currently almost all lesions are being treated to prevent the development of breast cancer. Breast conserving treatment followed by radiotherapy or in case of extensive lesions a mastectomy with or without immediate reconstruction are generally recommended. There is no consensus on the value of adjuvant hormonal treatment.

- **Outcome**

  The natural course of intraductal papillary carcinoma or papillary DCIS is largely unknown, as almost all lesions are treated. Fifteen years after DCIS diagnosis, including all subtypes, cumulative incidence of ipsilateral breast cancer was 1.9% after mastectomy, 8.8% after breast conservative surgery (BCS) plus radiotherapy, and 15.4% after BCS alone (Elshof et al. 2016).

  Despite the increased detection and treatment of these potential precursor lesions for breast cancer, the incidence of breast cancer has not declined, suggesting overdiagnosis exists resulting in overtreatment. Unfortunately, we cannot, at present, distinguish innocent from aggressive DCIS lesions regarding their capacity to progress to invasive breast cancer. Therefore, biomarker studies in order to enable risk stratification and prospective trials investigating the safety of a wait-and-see strategy for low-risk ductal carcinoma in situ have emerged.

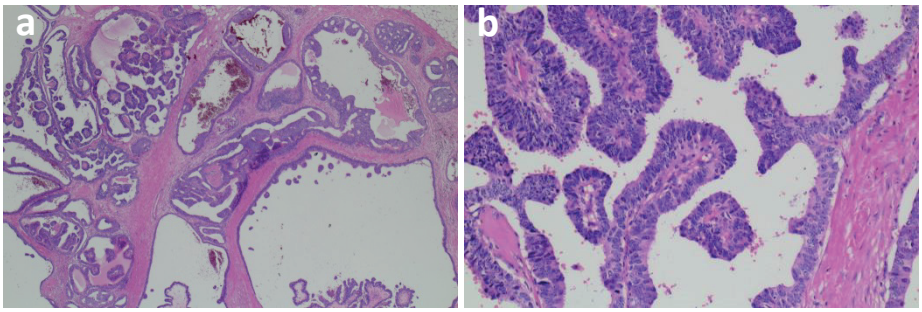
Macroscopy

As DCIS in general, intraductal papillary carcinoma is a segmental disease that can be associated with an impeccable breast parenchyma. Occasionally, dilated mammary ducts filled with necrotic debris and calcifications with or without fibrosis can be seen.

Microscopy

Intraductal papillary carcinoma is characterized by a segmental disease distribution. Involved spaces show intraluminal arborizing fibrovascular cores covered by neoplastic epithelium (Fig. 1a, Fig. 2-plate A1). In 1962, delicate and relatively inconspicuous fibrovascular cores were described as characteristic for malignant lesions such as intraductal papillary carcinoma (Kraus and Neubecker 1962). More recently however, others have refuted this statement, as they found broad fibrovascular cores even more often in malignant papillary lesions and concluded this morphologic feature was not a helpful feature to distinguish between benign and malignant lesions (Kraus and Neubecker 1962; Yamaguchi et al. 2014). The neoplastic epithelium often consists of one or more layers of uniform cuboidal to columnar epithelium with hyperchromatic nuclei of low to intermediate grade (Fig. 1b, Fig. 2-plate A2). Myoepithelial cells are absent within the fibrovascular cores but are seen at the periphery of the

involved spaces, in line with an in situ process. It should be noted that a pure papillary architecture is rarely seen, often it is seen intermixed with other growth patterns, such as micropapillary, cribriform, or solid DCIS.



Intraductal papillary carcinoma, Fig. 1 Intraductal papillary carcinoma, haematoxylin-eosin stain (H&E), (**a**) magnification x25; (**b**) magnification x200

Pitfalls

In some cases intraductal papillary carcinoma constitutes of a dimorphic epithelial cell population, in which an often basally located second population of cells with abundant pale cytoplasm ("globoid cells") is seen. These cells may be incorrectly interpreted as myoepithelial cells (Collins and Schnitt 2007). Immunohistochemical staining for epithelial and myoepithelial cells can resolve this issue and confirm the epithelial nature of these cells. Dislodgement and displacement of fragments from papillary lesions into the surrounding breast stroma or even within lymphatic vascular spaces, especially after a biopsy procedure, is a well-known occurrence and should be interpreted with caution (Collins and Schnitt 2007; Kraus and Neubecker 1962; Ni and Tse 2015). In case of displacement into the surrounding breast stroma, epithelial components with some degree of degenerative changes are present within the confines of the biopsy tract with concomitant reactive changes such as reactive fibrous stroma, signs of associated haemorrhage, fat necrosis and some degree of inflammation. Invasion should only be considered when epithelial structures are found well away from the biopsy site and show morphological features consistent with invasive cancer. Likewise, the presence of epithelial fragments in lymphatic vascular spaces or even lymph nodes should be doubted when no convincing invasive cancer is found elsewhere within the breast.

Immunohistochemistry to verify the presence or absence of myoepithelial cells in the distinction between true invasion and displacement is only useful when myoepithelial cells can be detected, because often only the luminal epithelial cells are displaced. Especially in intraductal papillary carcinoma where myoepithelial cells are only found at the periphery, immunohistochemistry is of limited value (Collins and Schnitt 2007; Ni and Tse 2015).

Immunophenotype

The neoplastic epithelial compartment often shows strong homogeneous staining for estrogen receptor (ER). To confirm the absence of myoepithelial cells within the papillary fibrovascular structures and the presence at the periphery of the involved spaces, a p63 stain is advised (see also below) (Fig. 2-plate A3, A4).

Molecular features

Few studies have evaluated molecular alterations in intraductal papillary carcinoma specifically, in line with its rarity and the uncertainty regarding what can be considered as such a lesion. In addition, most studies have looked at only small and nonuniform series, variably including atypical papillomas, papillomas with DCIS, intraductal papillary carcinomas or even invasive papillary carcinomas. Taking this into account, numerical or structural alterations in chromosome 17 and the accumulation of numerical alterations in chromosomes 3, 7 and X have been detected in a low percentage of the cases of papillary carcinoma, but not in papillomas (Tsuda et al. 1997).

A higher PIK3CA and AKT1 mutation frequency was found in papillomas compared to papillary carcinomas, which might suggest a different molecular origin of at least some papillary carcinomas (Troxell et al. 2009).

Whereas LOH at loci 16p13 and 16q21 could be detected in malignant as well as paired benign papillary lesions as obtained from adjacent tissue, LOH at locus 16q23 and at the TP53 locus was limited to malignant lesions, suggesting a role for the latter two in malignant transformation (Di Cristofano et al. 2005; Lininger et al. 1998). LOH at loci 16q12.2 and 16q21 was found exclusively in malignant intraductal papillary lesions in core needle biopsies. Therefore, these loci of LOH might be potential biomarkers in the differential diagnosis with benign lesions (Yoshida et al. 2012).

Differential diagnosis

Other forms of ductal carcinoma in situ

There is no evidence to date that the papillary growth pattern as seen in intraductal papillary carcinoma implicates relevant differences in terms of clinical or radiological features and outcome compared to DCIS lesions comprising other growth patterns. Of note, as described above, DCIS with a pure papillary growth pattern is rarely seen, but a clear definition of when to call a DCIS lesion “intraductal papillary carcinoma” as a whole is lacking (e.g., which percentage of the lesion should consist of a papillary growth pattern). Finally, labeling DCIS with a papillary growth pattern as intraductal papillary carcinoma may be relevant when considering a differential diagnosis with other papillary lesions; it can also be confusing as DCIS showing other growth patterns are simply diagnosed as DCIS.

Benign papilloma

Benign papillomas are either localized centrally (solitary) or in the periphery (multiple) and show a similar papillary growth pattern with variable degrees of cell proliferation. In benign papillomas, however, one cannot only appreciate the presence of myoepithelial cells along the periphery of involved lumina but within the fibrovascular structures as well. Also in the proliferative areas, a mixture of luminal epithelial cells and myoepithelial cells is seen, consistent with a hyperplastic process (Fig. 2-plate B1, B2, B3). A heterogeneous ER expression pattern is often seen (Fig. 2 -plate B4), but homogeneous ER expression does not rule out benignancy, especially when epithelium with columnar cell type change is encountered (Ni and Tse 2015). Other useful findings are the presence of apocrine metaplasia within a papillary lesion and usual ductal hyperplasia and sclerosing adenosis in the adjacent breast tissue, which are suggestive of a benign papilloma (Collins and Schnitt 2007; Kraus and Neubecker 1962).

When an undoubtedly neoplastic epithelial population with papillary growth has been identified one should keep in mind the following. A recognizable architecture of a benign papilloma in some part of the lesion precludes the diagnosis of intraductal papillary carcinoma and should rather be considered an atypical papilloma or a papilloma with DCIS depending on the classification used.

Encapsulated papillary carcinoma and solid papillary carcinoma

Encapsulated papillary carcinomas often have a symptomatic presentation with a subareolar mass and/or nipple discharge mostly occurring in elderly women. Microscopically, one or several nodules of often but not exclusively low to intermediate grade papillary neoplasms can be seen originating in a cystically dilated duct surrounded by a thick fibrous capsule (Collins and Schnitt 2007; Ni and Tse 2015). In contrast to intraductal papillary carcinoma, these lesions do not show a rim of myoepithelial cells at the periphery and ER is homogeneously and strongly expressed (Fig. 2-plate C1, C2, C3, C4).

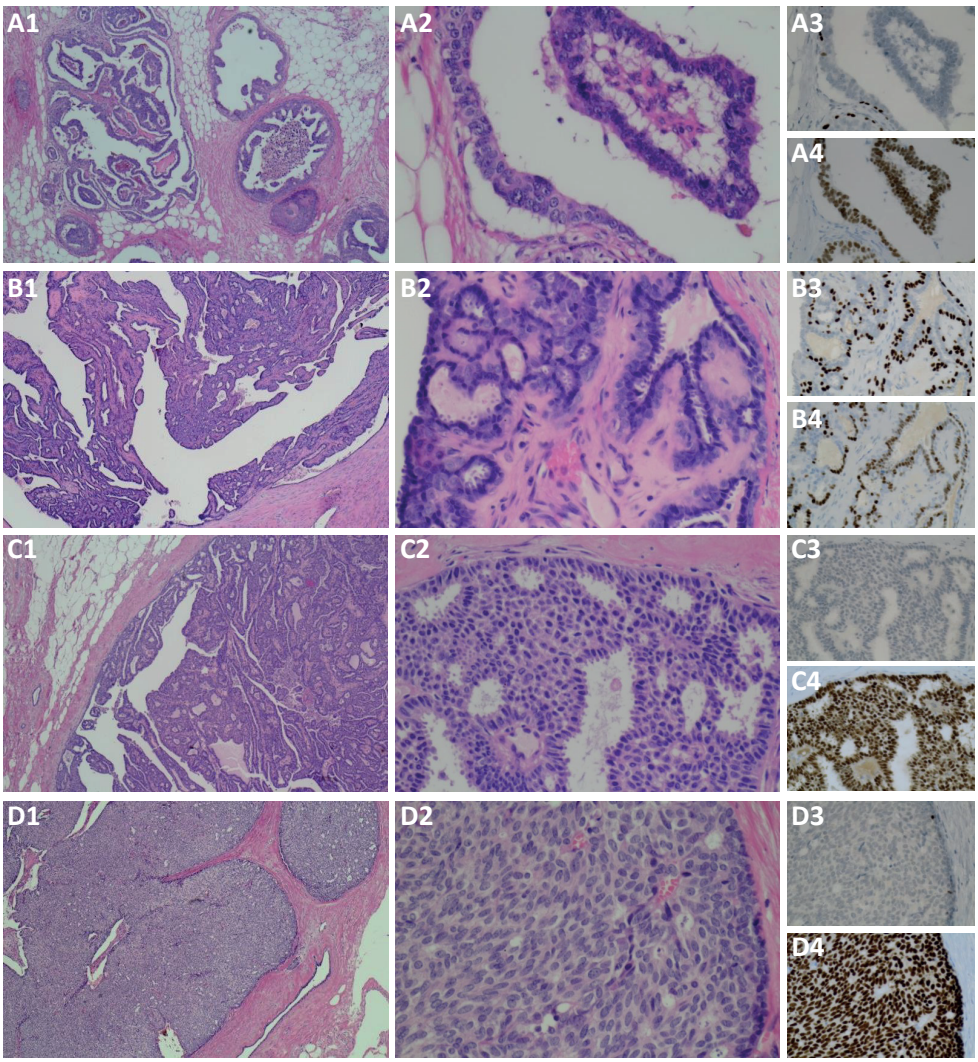
Solid papillary carcinoma also tends to present in elderly women as a circumscribed mass. As in intraductal papillary carcinoma a papillary ground structure can be appreciated in solid papillary carcinoma. In the latter, however, fibrovascular cores are often completely surrounded by a solid epithelial cell proliferation. These epithelial cells often show ovoid to spindle bland cells and can show neuroendocrine features, both morphologically and immunohistochemically, with the expression of neuroendocrine markers such as synaptophysin and chromogranin A. Mucin production or even a mucinous invasive component can be seen in association with these lesions. Myoepithelial cells can be present or absent at the periphery of these lesions while ER is homogeneously expressed in epithelial cells (Fig. 2-plate D1, D2, D3, D4).

The true nature of both these entities is uncertain. Historically, these lesions were considered variants of DCIS but given the often lack of myoepithelial cells, these lesions may perhaps be better classified as low grade invasive carcinomas with pushing growth or intermediates during the progres-

sion from in situ to invasive breast cancer. In the absence of a component of frank invasive growth or high-grade morphology, the outcome is excellent.

As described above the presence of myoepithelial cells both at the periphery (DD encapsulated/solid papillary carcinoma) and in the fibrovascular structures and/or cell proliferation (DD benign papilloma) is a key distinguishing feature. One should be careful interpreting immunohistochemical stains for myoepithelial cells as both stromal fibroblasts and pericytes can show cross-reactivity, and all stains have their inherent sensitivity and specificity. A combination of more than one marker is therefore advised. P63 is superior to other myoepithelial markers in the classification of papillary lesions, as it is a nuclear stain with only minimal cross-reactivity and high sensitivity. For evaluating the nature of solid epithelial proliferations often seen in papillary lesions, cytokeratin 5/6 is recommended, as among the high molecular weight cytokeratins (HMWCKs) it has the highest sensitivity and specificity (Ni and Tse 2015; Tse et al. 2009).

Classifying papillary lesions on fine-needle aspiration is challenging and should generally be discouraged, given the necessity to visualize not only the presence of myoepithelial cells but also their exact location within the lesion.



Intraductal papillary carcinoma, Fig. 2 (**a**) Intraductal papillary carcinoma: A1 – H&E x50; A2 – H&E x400; A3 – p63 x400; showing presence of myoepithelial cells at the periphery of the involved space but not within the fibrovascular structure; A4 – ER x400, strong diffuse homogeneous ER expression. (**b**) Intraductal benign papilloma: B1 – H&E x50; B2 – H&E x400; B3 – p63 x400, showing presence of myoepithelial cells both within fibrovascular structures and at the periphery of the involved space; B4 – ER x400, heterogeneous ER expression (mosaic pattern). (**c**) Encapsulated papillary carcinoma: C1 – H&E x50; C2 – H&E x400; C3 – p63 x400, showing no myoepithelial cells; C4 – ER x400, strong diffuse homogeneous ER expression. (**d**) Solid papillary carcinoma: D1 – H&E x50; D2 – H&E x400; D3 – p63 x400, showing sporadic myoepithelial cells at the periphery of the nodules; D4 – ER x400, strong diffuse homogeneous ER expression

Immunohistochemical biomarkers

Several studies have evaluated the effectivity of new immunohistochemical biomarkers to distinguish benign from malignant papillary lesions. The absence of staining for stem cell markers CD44 and CD133 may be useful in identifying malignant papillary lesions. Positive CD44 expression has been proposed as a marker to differentiate between benign and malignant papillary lesions with a reported sensitivity of 45% and a specificity of 92% (Tse 2005) and CD133 expression was significantly lower in papillary carcinomas than in benign or atypical papillomas ($p<0.001$) (Lin et al. 2014).

Cell cycle markers cyclin B1 and cyclin D1 have been shown to be independently associated with malignancy in papillary lesions. Positive staining for cyclin B1 and cyclin D1 was found to be helpful for identifying malignant papillary lesions with a sensitivity of 80% and a specificity of 72.7% for cyclin B1 and a sensitivity of 86.4% but only a specificity of 32.6% for cyclin D1 (Loh et al. 2015). The expression was however frequently heterogeneous and only focal, limiting its usefulness in clinical practice.

References and further reading

1. Collins, L. C., & Schnitt, S. J. (2007). Papillary lesions of the breast: selected diagnostic and management issues. *Histopathology*, *52*(1), 20–29. http://doi.org/10.1111/j.1365-2559.2007.02898.x
2. Di Cristofano, C., Mrad, K., Zavaglia, K., Bertacca, G., Aretini, P., Cipollini, G., et al. (2005). Papillary lesions of the breast: a molecular progression? *Breast Cancer Research and Treatment*, *90*(1), 71–76. http://doi.org/10.1007/s10549-004-3003-3
3. Elshof, L. E., Schaapveld, M., Schmidt, M. K., Rutgers, E. J., Leeuwen, F. E., & Wesseling, J. (2016). Subsequent risk of ipsilateral and contralateral invasive breast cancer after treatment for ductal carcinoma in situ: incidence and the effect of radiotherapy in a population-based cohort of 10,090 women. *Breast Cancer Research and Treatment*, *159*(3), 553–563. http://doi.org/10.1007/s10549-016-3973-y
4. Kraus, F. T., & Neubecker, R. D. (1962). The differential diagnosis of papillary tumors of the breast. *Cancer*, *15*, 444–455.
5. Lin, C.-H., Liu, C.-H., Wen, C.-H., Ko, P.-L., & Chai, C.-Y. (2014). Differential CD133 expression distinguishes malignant from benign papillary lesions of the breast. *Virchows Archiv*, *466*(2), 177–184. http://doi.org/10.1007/s00428-014-1695-2
6. Lininger, R. A., Park, W. S., Man, Y. G., Pham, T., MacGrogan, G., Zhuang, Z., & Tavassoli, F. A. (1998). LOH at 16p13 is a novel chromosomal alteration detected in benign and malignant microdissected papillary neoplasms of the breast. *Human Pathology*, *29*(10), 1113–1118.
7. Loh, S. F., Cooper, C., Selinger, C. I., Barnes, E. H., Chan, C., Carmalt, H., et al. (2015). Cell cycle marker expression in benign and malignant intraductal papillary lesions of the breast. *Journal of Clinical Pathology*, *68*(3), 187–191. http://doi.org/10.1136/jclinpath-2014-202331
8. Ni, Y.-B., & Tse, G. M. (2015). Pathological criteria and practical issues in papillary lesions of the breast - a review. *Histopathology*, *68*(1), 22–32. http://doi.org/10.1111/his.12866
9. Troxell, M. L., Levine, J., Beadling, C., Warrick, A., Dunlap, J., Presnell, A., et al. (2009). High prevalence of PIK3CA/AKT pathway mutations in papillary neoplasms of the breast. *Modern Pathology*, *23*(1), 27–37. http://doi.org/10.1038/modpathol.2009.142
10. Tse, G. M. K. (2005). CD44s is useful in the differentiation of benign and malignant papillary lesions of the breast. *Journal of Clinical Pathology*, *58*(11), 1185–1188. http://doi.org/10.1136/jcp.2005.026906
11. Tse, G. M., Tan, P. H., & Moriya, T. (2009). The role of immunohistochemistry in the differential diagnosis of papillary lesions of the breast. *Journal of Clinical Pathology*, *62*(5), 407–413. http://doi.org/10.1136/jcp.2008.063016
12. Tsuda, H., Takarabe, T., Inazawa, J., & Hirohashi, S. (1997). Detection of Numerical Alterations of Chromosomes 3, 7, 17 and X in Low-grade Intracystic Papillary Tumors of the Breast by Multi-color Fluorescence In Situ Hybridization. *Breast Cancer*, *4*(4), 247–252.
13. Yamaguchi, R., Tanaka, M., Tse, G. M., Yamaguchi, M., Terasaki, H., Nomura, Y., et al. (2014). Broad fibrovascular cores may not be an exclusively benign feature in papillary lesions of the breast: a cautionary note. *Journal of Clinical Pathology*, *67*(3), 258–262. http://doi.org/10.1136/jclinpath-2013-201749
14. Yoshida, M., Tsuda, H., Yamamoto, S., Kinoshita, T., Akashi-Tanaka, S., Hojo, T., & Fukutomi, T. (2012). Loss of heterozygosity on chromosome 16q suggests malignancy in core needle biopsy specimens of intraductal papillary breast lesions. *Virchows Archiv*, *460*(5), 497–504. http://doi.org/10.1007/s00428-012-1200-8