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**Pancreatic intraepithelial neoplasia – can we detect early pancreatic cancer?**

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Review

# Pancreatic intraepithelial neoplasia – can we detect early pancreatic cancer?

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Abbreviations: PDAC, pancreatic ductal adenocarcinoma; PanIN, pancreatic intraepithelial neoplasia; MCN, mucinous cystic neoplasm; IPMN, intraductal mucinous neoplasm; MUC, mucin; EUS, endoscopic ultrasound; COX, cyclooxygenase

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## Abstract

Pancreatic cancer is one of the most lethal cancers with an incidence equalling mortality. Pancreatic cancer is a heterogeneous group in which pancreatic ductal adenocarcinoma (PDAC) is the commonest. It is now established that PDAC develops through stepwise progression from precursor lesions. Detection and treatment of these precursor lesions would allow curative treatment. Three precursor lesions for PDAC have been identified. Two of these - mucinous cystic neoplasms (MCNs) and intraductal papillary mucinous neoplasms (IPMNs) - are rare, radiologically detectable, cystic precursor lesions which can be cured if treated at the pre-invasive stage. The third and commonest precursor lesion has recently been defined as pancreatic intraepithelial neoplasia (PanIN). PanINs are microscopic lesions with no clinical correlate. They display a spectrum of cyto-architectural changes (PanIN-1, PanIN-2 and PanIN-3) mirrored in an increasing accumulation of molecular genetic changes with PanIN-3 sharing many of the alterations with PDAC. The great advances in the understanding of pancreatic carcinogenesis have opened avenues for diagnosis and chemoprevention. However, access to the pancreas is limited, molecular tests are at the early stages and too little is known about the natural history of early PanINs to justify resection. Currently screening focuses on high risk individuals only.

## Introduction

More than 230 000 new cases of pancreatic cancer were diagnosed worldwide in 2002.<sup>1</sup> In the UK it is the 11<sup>th</sup> most common cancer with an annual incidence of approximately 7600 cases.<sup>2</sup> Pancreatic cancer is the fifth most common cause of cancer related death in the UK. With a five year survival rate of only 2-3% it presents one of the most lethal cancers with a mortality which essentially equals incidence.<sup>3</sup>

Despite many advances in modern medicine the prognosis of pancreatic cancer has remained very poor over the last two decades.<sup>4</sup> Approximately 85% of cases present at an advanced stage where curative surgical treatment is no longer possible. 15 - 20% of cases are treated surgically with a curative intent,<sup>5</sup> however disease recurrence is frequent and 5 year survival low at 7-25%.<sup>6</sup> Surgery is currently the only hope for cure. In many solid cancers detection and treatment of early or pre-invasive stages of the disease have significantly improved survival as has been well demonstrated with colorectal cancer, breast cancer and cervical cancer.<sup>7,8,9</sup> Pancreatic cancer presents a particular challenge with respect to detection and treatment of early stage disease or pre-malignant conditions. First of all, the disease commonly presents with symptoms only at an advanced stage.<sup>10</sup> Secondly, the pancreas is a difficult organ to access. Visualisation is often limited to cross-sectional imaging and ultrasound. Most pancreatic cancers show a highly infiltrative and partly discontinuous growth pattern rendering early radiological recognition difficult. Tissue biopsy sampling is restricted due to small size of the organ, its retroperitoneal location and risk of complications such as pancreatitis, fistula or metastatic implantation.<sup>11</sup>

The term pancreatic cancer is often used synonymously with pancreatic ductal adenocarcinoma (PDAC), which is by far the commonest primary malignant tumour of the pancreas.<sup>12,13,14</sup> However, most cases which are diagnosed as pancreatic cancer are advanced adenocarcinomas with a tubular (pancreatico-biliary) growth pattern arising in the head of the pancreas. They may not just have arisen from the pancreatic parenchyma but in a significant proportion also the distal common bile duct and in some cases the ampulla of Vater.<sup>15,16</sup> They may therefore represent a heterogeneous group of tumours with potentially different carcinogenetic pathways and pre-malignant conditions.

### **Pre-malignant epithelial lesions in the pancreas**

Of all primary pancreatic carcinomas PDAC and its variants account for approximately 90%.<sup>17</sup> Rare carcinomas such as pancreatic acinar cell carcinoma and its potential precursor lesions shall not be considered here. It is now established that PDAC develops through stepwise progression from pre-invasive lesions.<sup>18,19,20</sup> These precursor or “precancer” lesions provide a potential substrate for curative intervention. Evidence underscoring their nature as precursor lesions stems from several sources. Morphological studies have laid the foundation for our current understanding of carcinogenesis. Molecular genetic analyses confirm the close relationship between pre-invasive lesions and invasive carcinoma.<sup>21</sup> Genetically engineered mouse models allow recapitulation of stepwise progression from pre-invasive to invasive neoplasms.<sup>22</sup>

We currently recognise three precursor lesions for PDAC (Table 1).<sup>23</sup> Pancreatic intraepithelial neoplasia (PanIN) represents the most important and most common lesion. It is the main subject of this review and will be discussed in detail in

subsequent sections. Intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs) can also be associated with an invasive ductal type adenocarcinoma.<sup>24,25</sup> IPMNs and MCNs belong to the group of cystic tumours of the pancreas which account for only 5% of all primary tumours of the pancreas.<sup>26</sup> They are macroscopically cystic and display a continuous morphological spectrum which includes lesions with bland lining epithelium with little atypia (adenoma), lesions with moderate dysplasia (borderline), lesions with severe/high grade dysplasia (carcinoma in-situ) and invasive carcinoma.<sup>24,25</sup> The prognosis for non-invasive IPMNs and MCNs is excellent and detection and surgical intervention at the pre-invasive stage is curative.<sup>27,28</sup> The prognosis is poor for tumours with stromal invasion.<sup>29,30</sup> Due to their grossly cystic nature and mucinous cyst contents early detection is now facilitated by improved radiological techniques and cyst fluid examination including cytology.<sup>31,32,33</sup> It is vitally important to examine surgically resected mucin producing cystic tumours very thoroughly, in their entirety if possible, to exclude an invasive carcinoma which would require close follow-up and discussion of adjuvant therapy.<sup>23</sup>

Although IPMNs and MCNs share a macroscopically cystic nature and a similar spectrum of morphological changes of the epithelium they are two distinctly different entities. MCNs are very rare and in the Kiel series account only for 8% of all pancreatic cystic neoplasms reviewed.<sup>34</sup> MCNs occur almost exclusively in women. The mean age at diagnosis lies between 40 and 50 years; patients with non-invasive lesions tend to be younger by 5-10 years compared to patients with an invasive carcinoma. 90% of tumours arise in the body and tail of the pancreas and do not show any connection with the pancreatic duct system.<sup>23</sup> The histological identification of specialised ovarian type stroma is the defining feature.<sup>35</sup> The lining

epithelium is mucinous in type and these lesions resemble mucinous cystic tumours encountered in the ovary and liver.

IPMNs in contrast are the most common cystic tumour of the pancreas accounting for 24% in the Kiel series.<sup>34</sup> By definition, IPMNs involve the main pancreatic duct and/or its branches (main duct type and/or branch duct type). They show a slight male predominance and occur usually between the age of 60 and 70. 80% occur in the head of the pancreas.<sup>24</sup> We now distinguish four histological subtypes by the characteristics of the lining epithelium: a gastric foveolar type (MUC1-, MUC2-), an intestinal type (MUC1-, MUC2+ and CDX2+), a pancreaticobiliary type (MUC1+, MUC2-, CDX2-), and an oncocytic type (variable expression of MUC1 and MUC2).<sup>36,37</sup> The intestinal type is the commonest. It usually affects the main pancreatic duct and an associated invasive carcinoma would commonly be of mucinous/colloid type with a more favourable prognosis than conventional PDAC.<sup>36,38</sup> The pancreatico-biliary type is rarer and when invasive usually associated with conventional ductal type adenocarcinoma.<sup>36</sup> The gastric foveolar type often affects branch ducts and appears less commonly associated with an invasive tumour.<sup>36</sup> The oncocytic type is exceptionally rare.<sup>39</sup> Other very rare neoplasms which enter the spectrum of intraductal lesions with potential of invasive carcinoma have also been described such as intraductal tubular neoplasms which lack the mucin production typically observed with IPMNs.<sup>40,41</sup>

Like IPMN, pancreatic intraepithelial neoplasia is also an intraductal lesion but in contrast to IPMNs and MCNs PanINs are a microscopic finding with no clinical correlate. Their relationship with IPMNs will be discussed later.



## Pancreatic intraepithelial neoplasia – terminology and classification

Microscopic pancreatic duct lesions occurring in association with invasive ductal adenocarcinoma have been recognised and described for many decades.<sup>42</sup> Detailed studies examining surgically resected pancreases as well as autopsy material revealed a significantly increased incidence of atypical duct lesions in association with pancreatic carcinoma.<sup>43,44,45</sup> Atypical duct lesions were found more commonly in the head of pancreas and appeared to increase with age.<sup>46</sup> The development of invasive ductal adenocarcinoma in pancreatic remnants months and years following incompletely resected incidental atypical duct lesions in the context of other benign pathology provided further evidence supporting a progression model from duct precursor lesions to adenocarcinoma.<sup>47,48</sup>

However, systematic evaluation of these lesions was hindered by a lack of a unifying terminology. 70 different terminologies were used including duct lesions, flat or papillary hyperplasia or metaplasia with and without atypia, dysplasia and neoplasia.<sup>49</sup> The need for an international nomenclature and classification was addressed at the Pancreas Cancer Think Tank meeting in Utah, US, in 1999. At this meeting there was agreement to adopt the new terminology of pancreatic intraepithelial neoplasia (PanIN).<sup>49</sup>

A 3 tier system was established: PanIN-1, PanIN-2 and PanIN-3 (Table 2).

Classification criteria were agreed and photographic and diagrammatic illustrations compiled. PanINs were distinguished from normal ductal epithelium which is cuboidal to low columnar with amphophilic cytoplasm and no evidence of mucinous cytoplasm, nuclear crowding or atypia (Figure 1). PanINs were also separated from

squamous metaplasia which is replacement of the ductal epithelium by squamous epithelium without any atypia (Figure 2). PanIN-1 was divided into PanIN-1A and PanIN-1B. PanIN-1A is defined as a flat lesion composed of tall columnar cells with basally located nuclei and abundant supranuclear mucin. The nuclei are round to oval (Figure 3). PanIN-1B lesions show a papillary, micropapillary or basally pseudostratified architecture but are otherwise identical to PanIN IA (Figure 4). PanIN-2 may be flat but is mostly papillary. These lesions have nuclear abnormalities by definition which may include nuclear enlargement, crowding, pseudostratification, hyperchromasia and some loss of polarity. Mitoses are infrequent, non-luminal and not atypical. No cribriform areas or necrosis is seen (Figure 5). PanIN -3 is usually papillary or micropapillary but could rarely be flat. Cribriform changes, “budding off” of small clusters of epithelial cells into the lumen and necrosis may be seen. Cytologically these lesions resemble the cellular features of carcinoma with loss of nuclear polarity, nuclear irregularity, prominent (macro) nucleoli and mitoses which may be abnormal. Dystrophic goblet cells may also be seen (Figure 6).<sup>49</sup>

The new standardised classification of pancreatic ductal lesions has facilitated comparison of morphological and molecular genetic studies enhancing the evidence for the role of PanINs as precursors in the stepwise progression to ductal adenocarcinoma.

### **Molecular background**

Cancer is caused by progressive accumulation of cellular genetic changes which will eventually lead to uncontrolled growth.<sup>22</sup> Molecular alterations can be observed at the genomic (DNA), transcriptomic (RNA) and the proteomic (post-translational

protein expression) level.<sup>20</sup> Molecular changes can occur during the early phase of carcinogenesis (initiation) or late (progression). Changes at the genomic level can be chromosomal or affect cancer related genes directly.<sup>22</sup> Cancer related genes are divided in functionally different classes including oncogenes, tumour suppressor genes and caretaker genes.

It is thought that genomic instability caused by telomere shortening may be one of the earliest, initiating events occurring in pancreatic carcinogenesis.<sup>50</sup> Telomeres, short DNA sequence repeats present at the end of chromosomes, protect them from fusion during cell division. Extreme shortening or “telomere erosion” can cause chromosomal bridging during the mitotic anaphase leading to significant chromosomal rearrangement precipitating further genetic disarray.<sup>22</sup> Telomere shortening is found in over 90% of PanIN-1A and over 95% of all PanIN lesions and likely presents one of the major causes for gain of oncogenes and loss of tumour suppressor genes in the progression to ductal adenocarcinoma.<sup>50</sup> Loss of heterozygosity (LOH) presents genomic instability caused by loss of chromosomal material compared to normal. LOH of chromosome 9p and 17p occurs at high frequency in PDAC and pre-invasive atypical intraductal lesions (PanIN-3) with loss of 9p being an early event in the progression of PanINs.<sup>51</sup>

Oncogenes are genes which promote growth when activated. They act in a dominant fashion and can be activated by a variety of mechanisms including intragenic mutation and gene amplification.<sup>19</sup> The most important oncogene implicated in PDAC is KRAS. Its gene product is involved in cell cycle progression.<sup>52</sup> In one study over 80% of PDACs showed an activating point mutation of codon 12 of the KRAS2 oncogene on chromosome 12p.<sup>53</sup> A meta-analysis of mutations in the KRAS oncogene in PanINs observed in the context of PDAC found KRAS mutations in just

over one third of PanIN-1A lesions, over 40% of PanIN-1B lesions and almost 90% of PanIN-2 and PanIN-3 lesions which were combined due to their overall small number.<sup>54</sup> These findings suggest that KRAS mutation is one of the earliest genetic abnormalities in pancreatic carcinogenesis. While testing of the KRAS mutation by PCR can be performed on small samples, the clinical relevance as a diagnostic marker is limited as the mutation affects the earliest precursor lesions of PDAC and it also has been demonstrated in a significant proportion of duct lesions in normal pancreases (19-38%)<sup>55</sup> and chronic pancreatitis (26%).<sup>56</sup> KRAS mutation appears to be associated with smoking.<sup>56</sup> It does not appear to be present in pancreatic acinar cells and is only present in acinar-ductal metaplasia lesions in association with PanINs.<sup>57</sup>

Tumour suppressor genes contribute to tumour growth when inactivated. They are recessive and can be inactivated by intragenic mutation of one allele and loss of the other, homozygous deletion or epigenetic gene silencing by promoter methylation.<sup>19</sup> The commonest inactivated tumour suppressor genes implicated in pancreatic cancer are p16/CDKN2A/INK4A, TP53 and SMAD4/DPC4/MADH4.<sup>22</sup>

Inactivation of the p16 gene has been demonstrated in up to 98% of pancreatic carcinomas.<sup>58</sup> Lack of the p16 protein, detected by immunohistochemistry, has been shown in 30% of flat duct lesions (PanIN-1A), 27% of papillary lesions (PanIN-1B), 55% of papillary duct lesions with atypia (PanIN-2) and 71% of carcinoma in-situ (PanIN-3) which were associated with PDAC indicating that loss of function of p16 is a relatively early event in pancreatic carcinogenesis.<sup>59</sup> Patients with the familial atypical multiple mole melanoma syndrome have a germline mutation in the p16/CDKN2A gene with an up to 22 fold risk of pancreatic cancer<sup>60</sup> with a strong association with the p16-Leiden deletion.<sup>61</sup> Homozygous deletion of the

p16/CDKN2A/INK4A gene occurs in 40% of PDAC and in 30% the neighbouring gene MTAP is also affected.<sup>62</sup> Concordant loss of MTAP and p16 has also been demonstrated in 8% of PanINs.<sup>63</sup> The MTAP gene product methylthioadenosine is involved in the synthesis of adenosine and chemotherapeutic agents targeting the loss of MTAP protein might be effective in a proportion of pancreatic carcinomas.<sup>19</sup>

TP53 is a frequently inactivated tumour suppressor gene in many solid cancers and is inactivated in 50-75% of pancreatic carcinomas, usually by an intragenic mutation and loss of the second wild type allele.<sup>20,64</sup> TP53 protein is a critical checkpoint in the repair of DNA damage inducing cell apoptosis in cases of irreparability.<sup>22</sup> When the gene is mutated the resulting protein tends to be stable and positive immunohistochemical staining indicates a mutated protein. TP53 staining is observed in varying proportions of PanIN-3 lesions suggesting that loss of TP53 function is a late event in carcinogenesis.<sup>65</sup> DPC4/SMAD4/ MADH4 (DPC = deleted in pancreatic cancer) is a tumour suppressor gene which is affected in approximately 50% of PDACs and is rarely observed in other cancer types.<sup>66</sup> The DPC4 gene product, SMAD4, is involved in the transforming growth factor beta pathway. Immunostaining for SMAD4 protein expression is a sensitive method which will usually demonstrate loss of the protein if both copies of the gene are lost.<sup>67</sup> Positive SMAD4 staining is observed in PanIN-1 and PanIN-2 but its absence has been demonstrated in 30% of PanIN-3 lesions indicating a late event in pancreatic carcinogenesis.<sup>68,65</sup>

One of the care-taker/genome maintenance genes implicated in PDAC is BRCA2 which is associated with hereditary breast and ovarian cancer syndrome. An inactivating germline mutation with secondary loss of the second copy of the gene is

seen in <10% of PDAC.<sup>69</sup> BRCA2 inactivation has only been demonstrated in a single PanIN-3 lesion which may suggest that this is a late event in carcinogenesis.<sup>70</sup>

With regards to alterations on the transcriptomic level, small non-coding RNA molecules, micro-RNAs (mi-RNAs) have recently gained interest as potential markers and therapeutic targets in pancreatic cancer.<sup>71</sup> There are early indications that miRNA deregulation may be an early event in the development of pancreatic intraepithelial neoplasia.<sup>72</sup>

In addition to the described altered genes and their products changes in the expression levels of many other proteins and apomucins have been observed in PanINs and PDAC using immunohistochemistry and tissue micro-arrays. Cyclin D1, a cell cycle regulating protein, has been shown to be over-expressed in over 60% of PDAC<sup>73,74</sup> and has also been demonstrated in 27% of PanIN-2 and 57% of PanIN-3 lesions as an intermediate step in the carcinogenetic process.<sup>65</sup> The proliferation antigen Topoisomerase II alpha have been demonstrated in PanIN-3 lesions mainly as a late event in carcinogenesis.<sup>65</sup> Ki67 expression appears to increase with the degree of PanINs with over 20% labelling found in PanIN-3.<sup>65,75</sup> The tumour marker prostate stem cell antigen (PSCA) is not present in normal ducts but expressed in all PanINs and ductal adenocarcinoma. Mesothelin appears to be expressed mainly in invasive ductal adenocarcinoma and is only found in a smaller percentage of PanINs. Fascin is expressed in all PanINs but at a higher level in PanIN-2 and PanIN-3. 14-3-3 $\sigma$  is expressed in 85% of PanIN-3 lesions and 90% of ductal adenocarcinoma.<sup>65</sup> Cyclo-oxygenase 2 (COX-2), implicated in activating signalling pathways, appears to be progressively overexpressed in PanIN lesions and invasive carcinoma making it a potential target for chemopreventative therapy.<sup>76,77</sup> Matrix metalloproteinase-7 is

over-expressed in all PanIN lesions suggesting this is an early event in pancreatic carcinogenesis.<sup>78</sup>

The epithelial apomucin MUC1 is expressed in normal ductal epithelium, less seen in PanIN-1 lesions but is re-expressed in PanIN-2 (43%) and PanIN-3 lesions (85%).

The gastric foveolar mucin MUC5 is not seen in normal ductal epithelium but its expression is seen in the earliest PanIN lesions and persists through all stages.<sup>65</sup>

MUC2 is not seen in PanIN lesions but is expressed in intestinal type IPMNs and could be used as a potential tool in the differential diagnosis.<sup>65</sup> MUC4 is increasingly detected from lower PanIN lesions to invasive adenocarcinoma.<sup>79,80</sup>

Abnormal transcriptional activation of the embryonic signalling pathways Notch and Hedgehog have been reported in PanIN lesions and the altered gastric epithelial differentiation in early PanINs may be related to activation of Hedgehog signalling.<sup>20,81</sup>

Further evidence for the progression model of pancreatic cancer comes from genetically engineered mouse models with a mutant KRAS which show the spectrum of PanIN lesions as in the human with development of invasive carcinoma in <10% of cases. Additional TP53 mutation results in PanIN lesions and highly aggressive, lethal invasive adenocarcinoma.<sup>82,83</sup> The described molecular genetic abnormalities are summarised in Table 3.

### **Differential diagnoses**

PanIN lesions need to be distinguished from other duct lesions including IPMNs, reactive ductal changes and cancerisation of ducts.

## IPMN and PanINs

The current definition of an IPMN is a grossly visible, mucin producing, predominantly papillary or, rarely flat, epithelial neoplasm arising from the main pancreatic duct or branch ducts with varying degree of duct dilatation. These lesions are usually >10mm in diameter and include a variety of cell types with a spectrum of cytological and architectural atypia.<sup>84</sup> Features supportive of an IPMN are macroscopically visible papillae, macroscopically visible luminal mucin and tall papillae with stromal cores. In lesions <10mm deeper sections may reveal a connection to a larger duct lesion. Correlation with radiology may further help. PanINs are defined as microscopic duct lesions, usually involving ducts < 5mm in diameter, with flat or papillary cuboidal to columnar mucinous lining epithelium with varying cytological and architectural atypia. The duct diameter should be measured from basement membrane to basement membrane not including any periductal structures. In ducts only partially involved by PanIN the duct diameter should be used. PanINs can affect ducts >5mm, usually related to duct dilatation due to proximal obstruction. Careful sectioning of the duct system is recommended to assess lesions >5mm. PanINs affecting the main pancreatic duct will usually have less complex and tall papillary structures than main duct IPMNs. PanINs should be graded according to the highest grade in any given lesion.

These guidelines will allow distinction of PanINs from the most common IPMN of intestinal type in most cases. Positive MUC2 staining in intestinal type IPMNs can further support the diagnosis. In contrast undoubted morphological overlap exists between the gastric foveolar type IPMN and PanINs which share a morphologically identical epithelium and MUC5 positivity.<sup>36,84</sup> Gastric IPMNs involve branch ducts, are smaller and are often associated with adjacent PanIN like complexes.<sup>85</sup> They



share more molecular alterations with PanINs than intestinal type IPMNs.<sup>86</sup> There is also increasing evidence that intestinal and non-intestinal IPMNs follow different biological pathways.<sup>36,85,86,87</sup> These findings support suggestions that gastric IPMNs may in fact be large PanIN lesions and focal accentuation of a diffuse duct disease.<sup>27</sup> This would explain the difficulties frequently encountered in trying to distinguish PanINs from small gastric IPMNs. Until the relationship of non-intestinal IPMNs with PanINs is fully characterised the two lesions have to be distinguished using the above guidelines as best as possible. Furthermore, many IPMNs show several epithelial types and prediction of biological behaviour may be difficult.

### **Reactive changes and cancerisation of ducts**

The presence of numerous neutrophils in duct epithelium should alert to the possibility of reactive changes. In reactive duct epithelium the architectural changes of PanIN are usually absent. While enlarged the nuclei usually have smooth contours and finely dispersed chromatin.<sup>49</sup>

Cancerisation of pancreatic ducts in PDAC may be difficult to distinguish from PanIN-3 lesions. The close proximity of carcinoma to the duct and the abrupt transition from a highly atypical epithelium to normal duct epithelium favour cancerisation. Deeper sections may highlight the relationship of the duct with the carcinoma.<sup>49</sup>

### **Where do we stand in the quest for early detection and prevention of pancreatic cancer**

Not all “pancreatic cancers” are pancreatic ductal adenocarcinomas (PDACs). Pancreatic head cancer is a heterogeneous group which may encompass a not

insignificant proportion of carcinomas arising from the distal common bile duct and the ampulla.<sup>16,88</sup>

A progression model for the development of PDAC from well defined precursor lesions has been established, supported by morphological, molecular and mouse model experimental studies. However, there may well be other carcinogenetic pathways to PDAC.<sup>21,89</sup>

We now recognise that the commonest precursor to PDAC is a microscopic lesion, termed pancreatic intraepithelial neoplasia (PanIN). The other two lesions - mucinous cystic tumours (MCNs) and intraductal papillary mucinous tumours (IPMNs) – are rare, macroscopically cystic lesions. Cysts are increasingly detected due to improving radiological techniques and a multimodal approach including cyst fluid analysis and cytology may correctly identify mucin producing cystic tumours. Mucinous cystic tumours should always be removed. The management of IPMNs is more controversial. They can often be multifocal rendering a curative surgical approach more difficult. In general, they should be removed when >3cm, when they display mural nodules or show connection to the main pancreatic duct. However in-situ and invasive carcinomas have been detected with IPMNs <1cm.<sup>23</sup>

As illustrated, the detection of specific molecular abnormalities in pancreatic samples could potentially help to identify otherwise undetectable microscopic precursor lesions. Unfortunately, the pancreas is rather difficult to access for any samples. In addition, detection of genetic abnormalities of early carcinogenesis, such as KRAS, leaves the clinician with the dilemma that the currently poorly understood natural history of the earliest precursor lesions may not justify a pancreatic resection.<sup>22</sup>

However there is evidence that high grade PanINs may progress to carcinoma and surgery may be indicated.<sup>90</sup>

Detection of molecular abnormalities of early precursor lesions may also open avenues for chemoprevention of early pancreatic cancer. Currently, chemoprevention, such as COX-2 inhibitors, is studied in mouse models only.<sup>20,91</sup>

Furthermore, pancreatic cancer is too uncommon for a general population screening to be practical. Screening should focus on high risk individuals with a strong family history or a known germline mutation associated with an increased risk of pancreatic carcinoma. At least five genetic syndromes are currently known.<sup>23</sup> Several of the genetic syndromes are associated with a specific histomorphology which, when encountered, should raise the index of suspicion of a genetic basis.<sup>60</sup> It has also been observed that the patients with a strong family history of pancreatic cancer show multifocal PanINs with a characteristic lobulocentric atrophy which can be detected with EUS.<sup>92</sup>

There are still enormous barriers to overcome before PanINs, the commonest precursor lesions for the most common pancreatic carcinoma, can be clinically detected and appropriately treated. Reliable molecular screening tests and chemoprevention are a long time away. Nevertheless over the last decades there have been phenomenal advances in the understanding of pancreatic carcinogenesis. Screening of high risk individuals using high resolution imaging and molecular techniques may bring us one step closer to fighting one of the most lethal cancers of mankind.

## Conclusions for the practising pathologist

The vast majority of precursor lesions for PDAC will be encountered in pancreatic resection specimens. MCNs and IPMNs should be embedded entirely if possible to exclude any foci of invasive carcinoma.<sup>23</sup> PanINs will usually be an incidental finding in a pancreatectomy specimen, mainly in the context of neoplastic disease. Their detection has currently no clinical implication except for the presence of PanIN-3 at the pancreatic neck resection margin. As there is evidence that PanIN-3 can develop into invasive carcinoma the possibility of further surgery should be considered and discussed, particularly if PanIN-3 is found during frozen section assessment of the pancreatic neck resection margin.<sup>90</sup> It is also important to realise that PanINs, including PanIN-3, are not only present in relation to PDAC but have also been encountered adjacent to distal common bile duct adenocarcinomas and ampullary carcinomas. Their presence can therefore not be used reliably to type a tumour as PDAC.<sup>93</sup>

Diagnostic biopsies from the pancreas are infrequently obtained. EUS guided aspiration cytology is more commonly used in the assessment of pancreatic head lesions which does not allow a reliable distinction between PanIN-3 and invasive ductal adenocarcinoma. If a pancreatic biopsy is performed it will usually be in the context of a radiological lesion. Identification of isolated PanIN-3 in this context may also raise the question of surgery.

Although currently of limited clinical relevance, the accurate and consistent identification of PanINs in resection specimens and their distinction from cancerisation of ducts and IPMNs will facilitate systematic molecular and morphological studies. These will allow characterisation of the group of ductal

adenocarcinomas developing from PanINs and their distinction from pancreatic carcinomas that may follow different carcinogenetic pathways. This will open avenues for early detection and chemoprevention in the future.

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For Peer Review

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For Peer Review

Table 1: Precursor lesions of pancreatic ductal adenocarcinoma

	<b>Mucinous cystic neoplasms</b> <b>MCNs</b>	<b>Intraductal papillary mucinous neoplasms</b> <b>IPMNs</b>	<b>Pancreatic intraepithelial neoplasia</b> <b>PanINs</b>
<b>Average age</b>	40-50	60-70	Increasing with age
<b>Gender</b>	Almost exclusively Female	Male > Female	Male = Female
<b>Location in pancreas</b>	Tail and Body	Head >> Body/Tail	Head > Body/Tail
<b>Macroscopic features</b>	Grossly cystic	Grossly cystic with papillae Usually >10mm	Usually not grossly visible Usually <5mm
	Mucoid contents	Mucoid contents	
	No connection to duct	Connected to main and/or branch duct	
<b>Microscopic features</b>	Mucinous epithelium	Mucinous epithelium (gastric, intestinal, pancreatico-biliary, oncocytic type)	Mucinous epithelium (gastric foveolar type)
	Ovarian type stroma	Collagenous stroma	Periductal collagenous stroma
<b>WHO-Classification</b>	MCN – adenoma (mild dysplasia)	IPMN – adenoma (mild dysplasia)	PanIN-1A and PanIN-1B
	MCN – borderline (moderate dysplasia)	IPMN – borderline (moderate dysplasia)	PanIN-2
	MCN – carcinoma in-situ (severe dysplasia)	IPMN – carcinoma in-situ (severe dysplasia)	PanIN-3
	MCN – invasive carcinoma	IPMN – invasive carcinoma	PDAC

Table 2: Pancreatic intraepithelial neoplasia (modified from Hruban 2001<sup>49</sup>)

<b>Normal</b> (Figure 1)	Cuboidal to low columnar epithelium with amphophilic cytoplasm.  <u>No</u> mucinous cytoplasm, nuclear crowding or atypia.
<b>Squamous (transitional) metaplasia</b> (Figure 2)	Mature stratified squamous or pseudostratified transitional epithelium <u>without</u> atypia.
<b>PanIN-1A</b> (Figure 3)	Flat lesion with tall columnar cells with basally located nuclei and abundant supranuclear mucin.  Small round to oval nuclei.  Oval nuclei situated perpendicular to basement membrane.
<b>PanIN-1B</b> (Figure 4)	Papillary, micropapillary or basally pseudostratified architecture.  Otherwise identical to PanIN-1A.
<b>PanIN-2</b> (Figure 5)	Mostly papillary but can be flat.  Nuclear abnormalities must be present and may include some loss of polarity, nuclear crowding, enlarged nuclei, pseudostratification, nuclear hyperchromatism.  Mitoses rare, non-apical and not atypical.  True cribriform structures with luminal necrosis and marked cytological atypia generally <u>not</u> seen.
<b>PanIN-3</b> (Figure 6)	Usually papillary or micropapillary architecture; rarely flat.  True cribriforming, "budding off" of small clusters of epithelial cells into lumen and luminal necrosis suggestive of PanIN-3.  Loss of polarity, dystrophic goblet cells, mitoses including occasional abnormal forms, nuclear irregularities and prominent (macro) nucleoli.  Resembles carcinoma <u>without</u> invasion.

Table 3: Molecular genetic abnormalities in PanINs

(most important oncogene and tumour suppressor genes in red)

	Normal	PanIN-1A	PanIN-1B	PanIN-2	PanIN-3	PDAC
MUC1	◆			◆	◆	◆
Telomere shortening		◆	◆	◆	◆	◆
K-ras mutation		◆	◆	◆	◆	◆
PSCA		◆	◆	◆	◆	◆
MUC5		◆	◆	◆	◆	◆
Fascin		◆	◆	◆	◆	◆
MMP7		◆	◆	◆	◆	◆
P16				◆	◆	◆
Cyclin D1				◆	◆	◆
TP53					◆	◆
DPC4/SMAD4					◆	◆
Topo II $\alpha$					◆	◆
Ki67					◆	◆
14-3-3 $\sigma$					◆	◆
MUC4					◆	◆
Mesothelin						◆



## Figure Legend

**Figure 1.** Normal low columnar pancreatic ductal epithelium without atypia.

**Figure 2.** Mature squamous metaplasia replacing part of duct epithelium with adjacent transitional epithelium.

**Figure 3.** PanIN-1A: flat lesion with tall columnar, mucinous epithelium.

**Figure 4.** PanIN-1B: papillary architecture with tall columnar, mucinous epithelium.

**Figure 5.** PanIN-2: papillary architecture with pseudostratified tall columnar epithelium.

**Figure 6.** PanIN-3: Papillary architecture with cribriform areas and “budding off” of a small cluster of epithelial cells. Cells with marked loss of polarity, mitoses and prominent nucleoli.

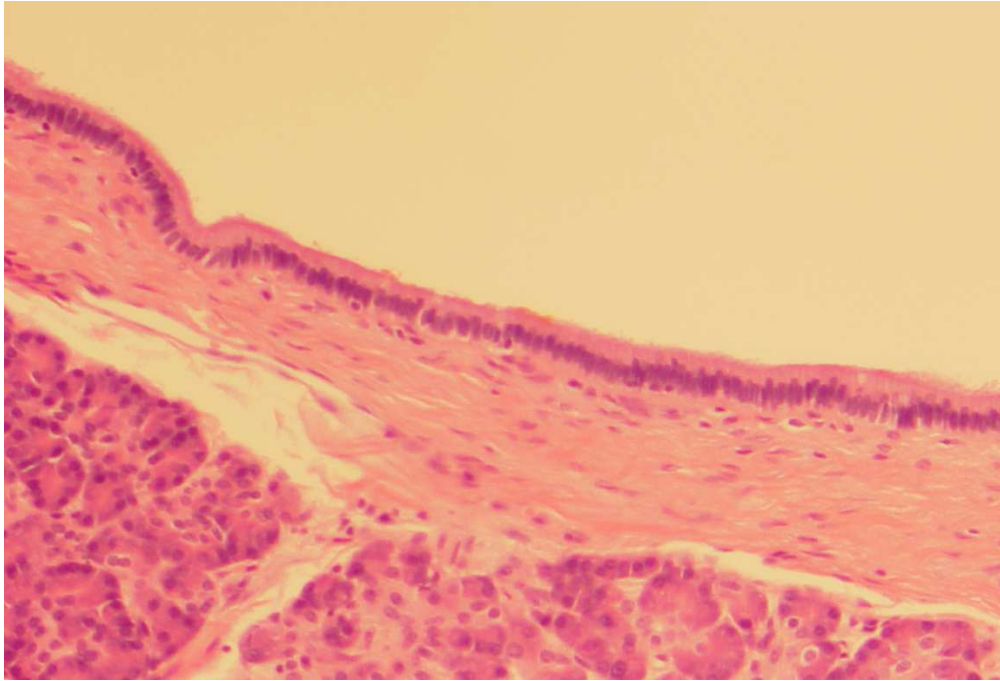


Figure 1. Normal low columnar pancreatic ductal epithelium without atypia.

Review

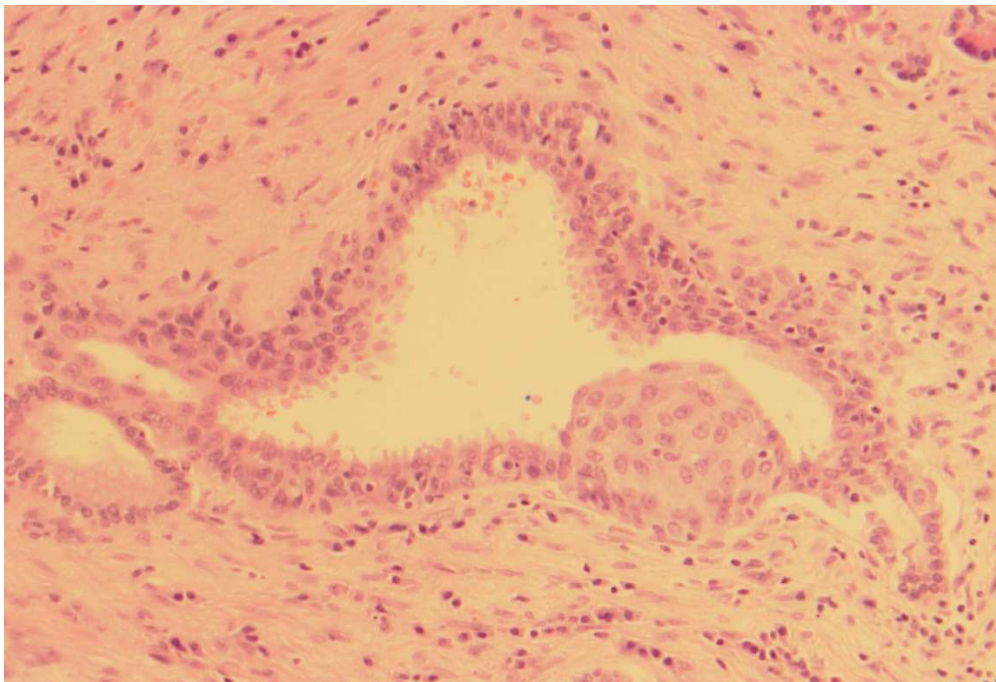


Figure 2. Mature squamous metaplasia replacing part of duct epithelium with adjacent transitional epithelium.

Review

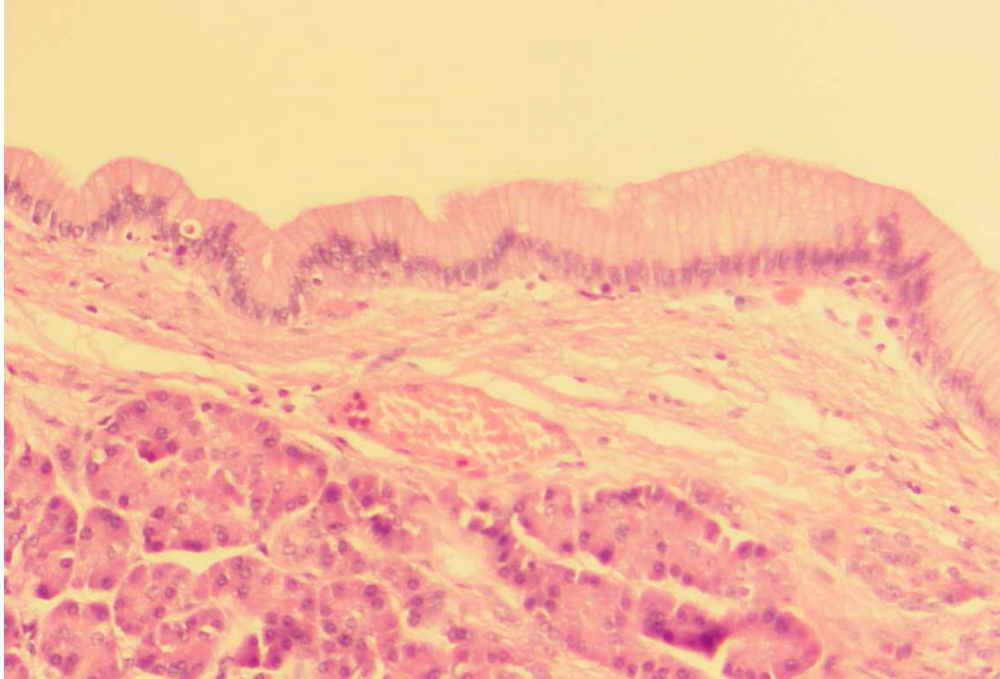


Figure 3. PanIN-1A: flat lesion with tall columnar, mucinous epithelium.

Review

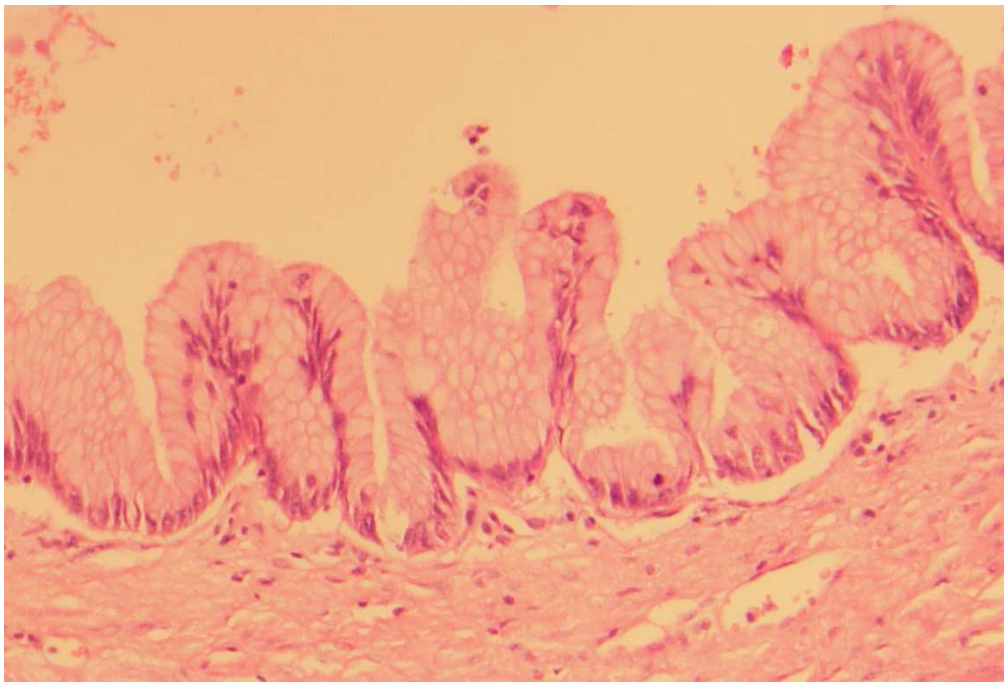


Figure 4. PanIN-1B: papillary architecture with tall columnar, mucinous epithelium.

Review

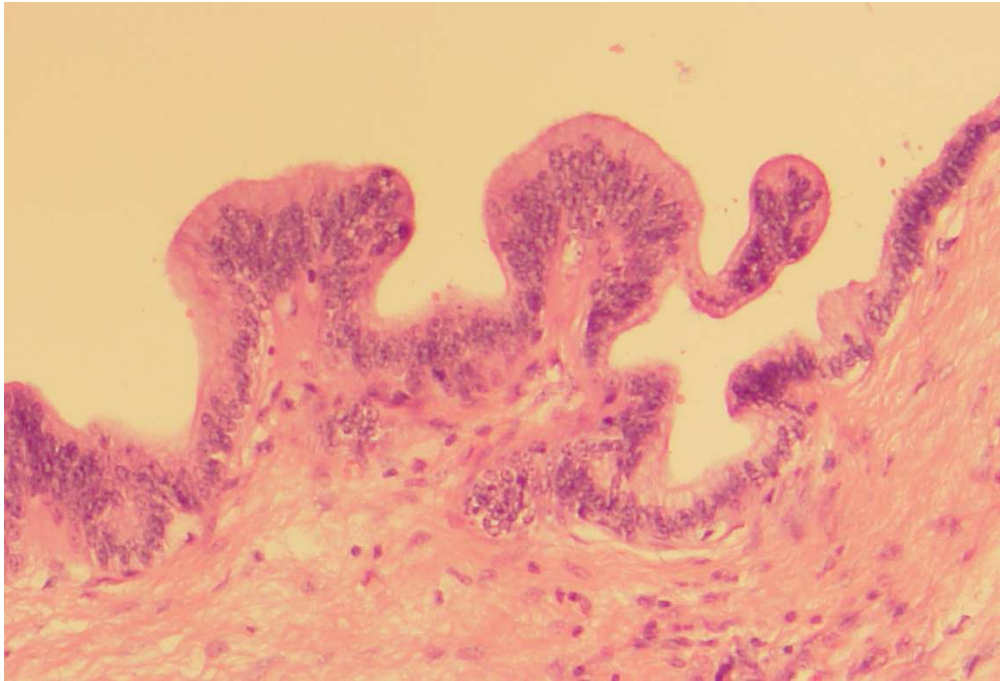


Figure 5. PanIN-2: papillary architecture with pseudostratified tall columnar epithelium.

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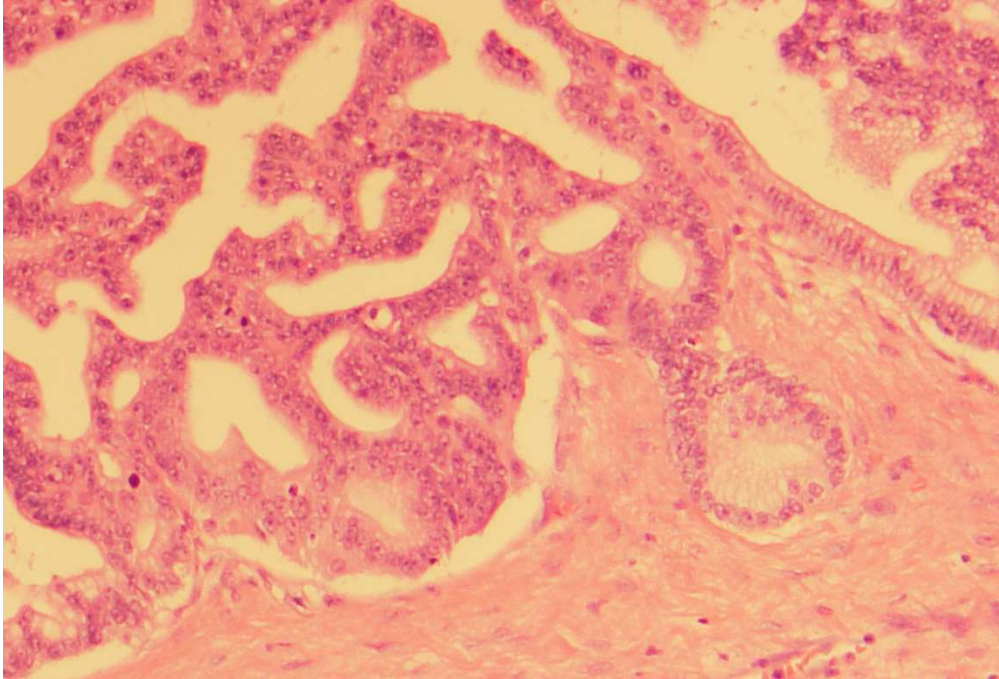


Figure 6. PanIN-3: Papillary architecture with cribriform areas and "budding off" of a small cluster of epithelial cells. Cells with marked loss of polarity, mitoses and prominent nucleoli.

Review