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Intraductal papillary mucinous neoplasms of the pancreas

A new approach to managing intraductal papillary mucinous pancreatic neoplasms

Paula Ghaneh, John Neoptolemos

Progress in the diagnosis and management plan for this pancreatic neoplasm

A large prospective study by Salvia *et al*[1] published in this issue of *Gut* shows that a follow-up protocol for branch duct intraductal papillary mucinous neoplasms (IPMNs) appears feasible and safe (***see page 1086***). IPMNs of the pancreas were originally described in a number of case reports and short series of patients in the early 1990s,[2 3] and mucinous cystic neoplasms of the pancreas had been reported in the 1980s.[4–6] In 1996 the World Health Organisation (WHO) revised the criteria for the pathological diagnosis of IPMN,[7] thus allowing the differentiation of IPMN from other mucinous/cystic neoplasms of the pancreas. This meant that a number of ''different'' neoplasms could now come under the single diagnostic umbrella of IPMN (table 1).

The apparent incidence of IPMN has increased dramatically over the past 10–15 years and now represents up to 10–20% of the pancreatic resection workload of specialist units.[8] This is due in part to improved imaging techniques, greater recognition of this clinicopathological entity and a larger number of asymptomatic patients undergoing cross-sectional imaging.[9]

Histologically, IPMNs progress along a pathway from adenoma to borderline IPMN with dysplasia to IPMN with carcinoma in situ and eventually to invasive carcinoma. It is not always possible to differentiate high-grade and low-grade lesions on imaging alone, and the time to progression is not known. The association of IPMNs (particularly the gastric type variant) with the precursor lesions of pancreatic ductal adenocarcinoma known as pancreatic intra-epithelial neoplasms (PanINs) or PanIN-like lesions may provide further information concerning their development.[10 11] Molecular analysis may provide biomarkers of disease progression in the near future with further follow-up of patients with characterised lesions. The expression of different mucins has been associated with prognosis in previous studies.[12] Various genetic and epigenetic alterations are associated with IPMNs (table 2). As with pancreatic ductal adenocarcinoma, point mutations of the K-ras oncogene occur in up to 80% of IPMN lesions, but in contrast to pancreatic ductal adenocarcinoma mutations of the tumour suppressor genes p53, p16 and SMAD4 occur less frequently or not at all (0–15%). IPMNs exhibit aberrant methylation at a variety of loci and there are certain upregulated genes demonstrated by microarray analyses.[13–15] These alterations tend to occur at higher frequency in IPMNs with an invasive component.

Certain inherited and familial syndromes have an association with IPMN, including Peutz-Jeghers syndrome and adenomatous familial polyposis.[16–19] IPMN is also associated with other extra-pancreatic malignancies such as colorectal cancer.[20]

Because of its variable malignant potential, the diagnostic and therapeutic challenge presented by IPMN is a singular one. The main questions are: who requires surgery and who does not and who can be followed up safely and, if so, what should the follow-up involve? In this issue of *Gut*, Salvia *et al*[1] attempt to answer this important question or at least provide further evidence to support critical clinical decisions. This paper reports on the follow-up of 109 patients with branch duct IPMN (BD-IPMN). Their diagnostic methods reflect the current standards for IPMN, as described in the following paragraphs, including clinical symptoms and imaging techniques such as magnetic resonance cholangiopancreatography (MRCP).

Most IPMNs occur in the head of the pancreas (>60%) and represent around 1% of pancreatic neoplasms.[21] Patients may present with abdominal pain, jaundice, weight loss, acute pancreatitis or

Table 1 Classification and characteristics of intraductal papillary mucinous neoplasms (IPMNs)

Classification	Adenoma
	Borderline
	Carcinoma in situ
	Invasive carcinoma
Histology	Tall columnar mucin-containing epithelium with or without papillary projections
	Involves main pancreatic duct (MD-IPMN) and/or side branch (BD-IPMN)
	Intestinal and gastric types
Differs from MCN	No ovarian stroma
Includes previously described tumours	Papillary carcinoma
	Ductectatic mucinous cystadenoma
	Villous mucinous adenoma
	Mucin-producing tumours of the pancreas
	Intraductal papillary mucinous tumours (IPMT)

MCN, mucinous cystic neoplasm.

Table 2 Examples of molecular alterations associated with intraductal papillary mucinous neoplasms (IPMNs)

Type of gene	Gene	Alteration	Comment
Oncogenes	K-ras	Mutation	47–80%
	BRAF	Mutation	3%
Tumour suppressor genes	p53	Overexpression	8%
	p16	LOH	0%
	SMAD4	LOH	0–15%
	STK11	LOH	>30%
Developmental genes	SHH	Overexpression	Higher expression than pancreatic ductal adenocarcinoma and chronic pancreatitis
Miscellaneous	Lipocalin 2	Overexpression	–
	CXCR4	Overexpression	Expressed in 31% IPMNs but not normal; 44% in invasive and 17% in non-invasive
	Galectin 3	Overexpression	–
	Claudin 4	Overexpression	100% in invasive; 29% in non-invasive
	Cathepsin E	Overexpression	–
	Trefoil factor family (TFF)	Overexpression	–
	S100A4	Overexpression	38% in invasive; 0% in non-invasive
	Mesothelin	Overexpression	43% in invasive; 0% in non-invasive
	ppENK	Hypermethylation	Higher frequency in high-grade (in situ carcinoma) than in low-grade (adenoma/borderline) IPMNs
	p16	Hypermethylation	
	Cyclin D2	Hypermethylation	50%
	TFP-2	Hypermethylation	60%
	SOCS-1	Hypermethylation	6%

Partly adapted from references 13–15.
LOH, loss of heterozygosity.

endocrine and/or exocrine insufficiency, or patients may be asymptomatic with an incidental diagnosis of IPMN. The diagnosis of IPMN relies on imaging to reveal typical features such as irregular dilation of the main pancreatic duct, a gaping ampulla (with copious mucin production), cystic lesion(s) communicating with the main pancreatic duct or side branches, or filling defects in the pancreatic duct. Multi-detector CT scanning, MRCP, endoscopic retrograde cholangiopancreatography and endoluminal ultrasound (EUS) are all useful in the diagnosis of IPMN.[22 23] Analysis of cyst fluid for mucin, carcinoembryonic antigen and estimation of serum CA19.9 may also add further diagnostic value.[24 25] The study by Salvia *et al*[1] secured a diagnosis of BD-IPMN using transabdominal ultrasound and MRCP. Criteria for a suspicion of malignancy were cyst size >3.5 cm, the presence of nodules and/or a thick wall, serum levels of CA19.9 >25 U/l, recent onset of diabetes mellitus or worsening of diabetes mellitus and/or the presence of clinical symptoms.

Once the diagnosis of IPMN is made, surgery is the main therapeutic option because of the risk of malignant transformation but, until recently, it has not been possible to separate lesions with relatively different risks of progression. This is important as these patients are often in their sixth or seventh decade and the risks of surgery are not inconsiderable.[26] At the present time patients with a main duct (MD)-IPMN should be offered surgery if they are fit. The type of resection will depend on the distribution of the lesions. Most lesions occur in the head and will entail a pylorus-preserving or classic Kausch-Whipple resection, whereas lesions of the tail will require a left pancreatectomy. At the time of surgery, frozen sections must be sent from the resection margin. This will dictate whether further pancreatic resection and possible total pancreatectomy is required. Patients with invasive IPMN who have positive resection margins have disease recurrence rates of over 50% and poor long-term survival.[27] Thus, all patients must be made fully aware that a planned partial pancreatic resection may need to be converted to a total pancreatectomy depending on the result of the intraoperative frozen section. Patients who have undergone resection for invasive IPMN have 5 year survival rates of 13–78%. The survival for those with non-invasive IPMN at the time of resection can be up to 90% or 100% (table 3).[7 21 26 28–32] The role of adjuvant treatment following resection for invasive IPMN has not been established.

Prognostic factors which are significant following resection for IPMN include lymph node involvement, the presence of invasive IPMN, neural and vascular invasion, resection margin status (for invasive IPMN) and whether there is MD-IPMN or BD-IPMN.[7 21 26 28–32]

Using the above mentioned diagnostic criteria, the 109 patients with BD-IPMN in the study by Salvia *et al*[1] were divided into two groups, one of 20 patients thought to be at high risk for malignancy and therefore suitable for resection, and 89 patients thought to be low risk. Of the 20 patients who had a resection, 2 (10%) had invasive carcinoma and eventually developed hepatic metastases and died 20 and 40 months after resection. It is interesting that none of the asymptomatic patients who underwent surgery had invasive carcinoma or carcinoma in situ. The overall follow-up for this arm was a median of 44.5 months.

Eighty-nine patients were followed up with either EUS or MRCP at 6 monthly intervals. These patients were asymptomatic and, interestingly, approximately two-thirds had multifocal disease. After a median follow up of 32 months, five patients underwent resection because their lesions increased in size (none had invasive carcinoma), two died of myocardial infarction at 60 and 50 months after the first observation, and the rest are still under follow-up and remain asymptomatic.

Because surgical intervention may be associated with a high morbidity rate[26] and IPMNs have a variable malignant potential, there has been considerable interest in the possibility of a safe follow-up protocol for patients with non-invasive IPMN. Patients with BD-IPMN exhibit lower rates of invasive disease and also better survival than those with MD-IPMN, even with limited resections.[28 33] It would seem reasonable that follow-up protocols for the present should focus on these patients. The International Association of Pancreatology (IAP) guidelines[34] recommend yearly follow-up for BD-IPMN lesions <10 mm in size, 6–12 monthly for those 10–20 mm in size and 3–6 monthly for lesions >20 mm.

There are very few prospective series of follow-up protocols that have long-term results on a reasonable number of patients, which is why the paper by Salvia *et al*[1] is important and provides good evidence that adopting a protocol based on the IAP guidelines can work in a carefully diagnosed and monitored group of patients. The strengths of this paper are that it is a prospective study with a large number of patients, the accuracy of the diagnosis was impressive (confirmed by a 100% correct diagnosis of IPMN in those patients who were resected) and complete follow-up data were available. The main drawbacks are that adopting this protocol may lead to overtreatment as only 10% of patients (in the resection group) had invasive carcinoma (the presence of symptoms appears to be extremely important in this group of patients) and the median follow-up in the asymptomatic

Table 3 Survival rates following resection for IPMNs

Series	No of patients	IPMN type	Median survival time (months)	Survival time (%) 1 year	2 year	5 year
Winter *et al*[8]	90	IPMN carcinoma	38	74	56	48
Serikawa *et al*[28]	45	MD-IPMN (21 carcinoma)	–	97	–	78
	56	BD-IPMN (7 carcinoma)	–	100	–	–
Fujino *et al*[26]	19	IPMN	–	–	–	91
	38	IPMN (carcinoma)	–	–	–	13
Wang *et al*[29]	39	IPMN (includes ? no of carcinoma)	21.5	–	–	69.8
Wada *et al*[30]	75	IPMN	–	–	–	100
	25	IPMN (carcinoma)	–	–	–	46
Sohn *et al*[31]	84	IPMN	–	97	94	77
	52	IPMN (carcinoma)	–	72	58	43
Salvia *et al*[32]	80	IPMN	–	–	–	100
	58	IPMN (carcinoma)	–	–	–	60
D'Angelica *et al*[21]	63	IPMN (30 carcinoma)	–	–	–	60

IPMN, intraductal papillary mucinous neoplasm; MD-IPMN, main duct intraductal papillary mucinous neoplasm; BD-IPMN, branch duct intraductal papillary mucinous neoplasm.

group is only 32 months. A much longer follow-up period will be required before stronger recommendations can be made, so further prospective studies with substantial follow-up times are still needed.

Nevertheless, at the present time, surgery should be recommended for patients with MD-IPMN. Those patients with BD-IPMN who are symptomatic or exhibit features which fulfil the criteria for a high suspicion of invasive IPMN (cyst size >3.5 cm, nodules and/or a thick wall, raised serum CA19.9 level) should also be offered surgery. The remaining patients with BD-IPMN may be followed up at 6–12 monthly intervals using non-invasive imaging such as MRCP, EUS or CT and serum CA19.9 estimation.

The study by Salvia *et al*[1] relied on radiological and endoscopic procedures and tumour marker analysis. Future studies should be designed to include molecular markers to add an extra component to the protocol. Several studies have assessed molecular markers. In one study, methylated ppENK was detected in four (44%) of nine samples of pancreatic juice from patients with high-grade (carcinoma in situ) but not in pancreatic juice samples from two patients with low-grade (borderline) IPMNs.[35] The expression of two or more of the four proteins S100A4, mesothelin, claudin 4 and CXCR4 was commonly observed in IPMNs with an invasive carcinoma (16 [73%] of 22 invasive IPMNs) but was not seen in any of 16 IPMNs without an invasive phenotype.[12] Nakamura *et al* reported that prognosis of IPMN was associated with mucin production.[11] The subset of IPMNs expressing gastric type mucin (MUC5AC) had the most favourable prognosis, and the subset of IPMNs expressing intestinal type secretory mucin (MUC2) had a better prognosis than that of IPMNs expressing membrane-bound type mucin (MUC1).[11]

In a relatively short period of time the diagnosis and management plan of this pancreatic neoplasm has progressed at an encouraging rate. Advances in diagnosis and surgical approaches have improved the outlook for these patients, and in the near future it is anticipated that the contribution of the underlying molecular and genetic mechanisms of this disease will further impact on clinical management.

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Lipids and HCV

Do high lipids help clearance of hepatitis C?

Stephen Ryder

High triglyceride levels may be a factor in the high rate of spontaneous clearance of HCV

A large volume of evidence suggests that lipids and lipid receptors are important in hepatitis C infection.

Hepatic steatosis is common, with at least 65% of liver biopsy specimens demonstrating steatosis. In genotype 3 infection, a specific mechanism of steatosis induction exists, via core antigen expression. The incidence of diabetes is higher in hepatitis C virus (HCV) infection and increases with increasing severity of liver disease. The mechanism of this is via insulin resistance, but it is uncertain whether hepatic steatosis is a result of the insulin resistance or plays a pivotal role in its induction.

HCV is associated with lipid in the serum and almost certainly uses lipid receptors to enter hepatocytes. The low-density fractions of serum contain HCV RNA particles and lipoviral particles (LVP) associated with triglyceride (TG)-rich lipoproteins. Such particles rich in TG have been shown to contain viral capsid and RNA.[1] TG is contained within chylomicrons or within very low-density lipoprotein (VLDL). Chylomicrons are synthesised in the intestine and transported via lymph into the circulation where they are broken down by the action of lipoprotein lipase in many cell types. The chylomicron remnant is then taken up by the liver via the low-density lipoprotein (LDL) receptor (LDLr) or the LDL receptor-related protein. Chylomicrons contain apolipoprotein B48 at the time of synthesis and later acquire apolipoprotein E (ApoE).

VLDL is synthesised in both liver and intestine, and, whatever the origin, is degraded by lipoprotein lipase-producing remnants. In man, these are primarily hydrolysed to form LDL. Some VLDL remnants may be taken up directly by the liver.

Upregulation of the LDLr increases the entry of HCV-LVP into hepatocytes, and binding of HCV-LVP can be blocked by anti-apolipoprotein B (anti-ApoB) and anti-ApoE.[2 3] Endocytosis of HCV can be mediated by LDLr,[4] which normally transports two different classes of cholesterol-containing lipoprotein particles into cells: LDL, which contains a single copy of ApoB-100, and VLDL, which contains multiple copies of ApoE.

An alternative lipid-based entry site for HCV in liver has been established using retrovirus/HCV pseudovirus particles.[5] These experiments suggest that attachment to hepatocytes is via a scavenger receptor protein, SR-B1, with cell entry via a coreceptor CD-81. SR-B1 is a component in the reverse cholesterol transport pathway, and recognises a number of lipoproteins, including high-density lipoprotein, LDL, VLDL and oxidised LDL.

ApoE, a ligand for both LDLr and SR-B1, has three major isoforms, Apo-E2, Apo-E3 and Apo-E4. These differ from one another by single amino acid substitution with marked differences in function. Apo-E3 has normal function, whereas Apo-E2 binds poorly to LDLr and Apo-E4 down regulates LDLr.[6]

A study of *APOE* gene polymorphisms in HCV infection suggested decreased severity of liver disease in patients with the E4 allele,[7] and ApoE2 and ApoE4 alleles have both been associated with an increased likelihood of viral clearance.[8] Both these alleles could help enhance viral clearance as the E2 allele binds poorly to LDLr and E4 down regulates it. Such defective binding could result in poor uptake of HCV-LVP into hepatocytes, with a resultant decrease in replication of the virus, favouring clearance of the virus before chronic infection can be established.

Changes in serum lipid profiles in chronic HCV infection are well described, serum cholesterol is significantly lower than in people not infected with HCV,[9] markedly more so in HCV genotype 3 infection.[10] This seems to be a definite effect of the virus as it reverses after successful treatment. The low cholesterol levels are associated with a decrease in ApoB levels in comparison with healthy controls, and ApoB levels negatively correlate with hepatic steatosis and viral load.[11]

In this issue of *Gut*, Marzouk *et al*[12] (***see page 1105***) show that in a rural Egyptian population with a high incidence of hepatitis C infection, the chance of clearing HCV infection was significantly greater in patients who had high TG levels. Unlike cholesterol levels that were lower in patients with chronic HCV infection but the same in uninfected controls and in patients who had spontaneously cleared HCV, TG levels were substantially lower in patients with chronic HCV infection than in uninfected individuals (102 vs 121 mg/dl), but those