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Surgical Aspects of Intraductal Papillary Mucinous Neoplasms of the Pancreas

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Rezumat

Aspecte chirurgicale ale neoplasmelor mucinoase papilare intraductale ale pancreasului

Neoplasmul mucinos papilar intraductal (IPMN) joacă un rol important în cadrul tumorilor exocrine ale pancreasului, din diverse motive. Deși reprezintă doar 1% din totalitatea tumorilor, acesta acoperă 20-30% din totalitatea neoplasmelor cistice, un grup definit histologic ce se bucură în ultimul timp de tot mai multă atenție. Neoplasmele mucinoase papilare intraductalecu originea în ductele pancreatice principale sau secundare prezintă rate de transformare malignă, prognostic și, prin urmare, indicații chirurgicale remarcabil de diferite. Prognosticul carcinoamelor ductale dezvoltate din IPMN nu diferă de cel al adenocarcinomul ductal 'clasic', cu o rată de supraviețuire la 5 ani foarte slabă (10%). Cu toate acestea, prognosticul IPMN poate totuși fi privit ca favorabil, deoarece rata ante-menționată poate ajunge până la 70% dacă tumora este non-invazivă. Acest aspect determină importanța diagnosticării și rezecării IPMN înainte ca acesta să sufere o transformare malignă în carcinom invaziv.

Cuvinte cheie: neoplasmul mucinos papilar intraductal, pancreas

Abstract

Intraductal papillary mucinous neoplasms (IPMN) play an important role amongst exocrine tumours of the pancreas due to several causes. Although they count for only 1% of all the tumours, they represent some 20-30% of all cystic neoplasms, a histologically defined group that has gained a lot of attention lately. IPMNs of the main or the secondary (branch) pancreatic ducts have remarkably different rates of malignant transformation, prognosis and thus indication for surgery. Prognosis of a ductal carcinoma developing from IPMN does not differ from 'classic' ductal adenocarcinoma, with a very poor (10%) 5-year survival rate. However, prognosis of IPMN can still be regarded favourable, because the above rate can be as high as 70% if the tumour is non-invasive. This fact leads to the importance of diagnosing and resecting IPMN before its malignant transformation into an invasive carcinoma.

Key words: intraductal papillary mucinous neoplasm, pancreas

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Introduction

Indications for surgery of pancreas tumours have changed greatly in the past 20 years. State-of-the-art radiology imaging and evolving diagnostic measures led to diagnosing surgically removable borderline or precancerous incidentalomas in the pancreas too. Naturally, more sophisticated surgical techniques played an important role as well in developing bolder and more liberal indications for pancreas resections with reasonable mortality (less, than 5% in experienced surgical departments).

Retrospective analysis of CT and MR images show that the

rate of incidental finding of cystic pancreatic pathologies is 2-4% in the population above 50 years. Upon investigating 600 MR examinations, Lee and al. found that the prevalence of pancreatic cysts was 13.5% with an average size of 7 mm. (1) Majority of these are benign pseudocysts, however, 20% of them turn out to be cystic pancreatic tumours such as serous or mucinous cystadenomas, cystadenocarcinomas, solid pseudopapillary neoplasms or intraductal papillary mucinous neoplasms.

When dealing with pancreas pseudocysts, it is important to rule out the possibility of the presence of a cystic tumour. What are the signs of a possible underlying malignancy? The following are the key features: if the patient has no background history of pancreatitis, if the rest of the pancreas has normal CT appearance, if the tumour markers are elevated, if sample from the cystic fluid has normal amylase levels or it has suspicious cytological characteristics, or if radiology imaging shows a multi-locular cyst with contents keeping with mucin. Differential diagnosis of mucinous and non-mucinous cysts is of utmost importance. Endoscopic ultrasound can be the most valuable aid of the clinician in this matter.

Inadequate management or surgical treatment is relatively common if a mucinous tumour is mistaken for a pseudocyst. *Figure 1* shows the specimen after pancreas resection, where a supposed pseudocyst observed for two years turned out to be an IPMN already with high grade dysplasia. A cysto-gastrostomy was performed in another suspected pseudocyst case, where the final diagnosis was again IPMN, as seen on *Figure 2*. Creating a connection between the stomach and the IPMN obviously did not relieve the symptoms of the patient.

IPMN, after all, is an intraductal proliferation of mucin secreting pancreas cells resulting mainly in papillary growth and duct ectasia. Average age group of its prevalence is 65-68 years with a slight male predominance. Although the first documentation of the disease was three decades ago, its classification was only introduced in WHO nomenclature in 1996. The first, so called Sendai consensus guideline dates back to 2006 while the modified guideline was published six years later, in 2012. (2, 3) Relevant data for the frequency of IPMN can only be estimated since we take this diagnosis into account. The incidence was around 4-5/100.000 patients after the millennium, according to a retrospective study carried out in Mayo Clinic. (4)

The key features we need to understand in differential diagnosis are: intraductal growth and thick mucin secreted by the tumour itself lead to sings of duct obstruction with consecutive dilatation of the duct, thus causing exocrine or even endocrine pancreas insufficiency. Signs and symptoms can mislead the clinician towards the impression of chronic pancreatitis, however the correct diagnosis can be suspected even by the endoscopic appearance of the papilla. A prominent papilla with mucinous discharge from the ampulla of Vater can only mean the presence of a mucinous tumour connected with the ducts. Besides, ERCP can indicate the segmentally dilated duct system. CT scan is less specific, it is more useful in identifying the size of the IPMN and the extent of duct dilation. The so-called branch-duct IPMN can be diagnosed

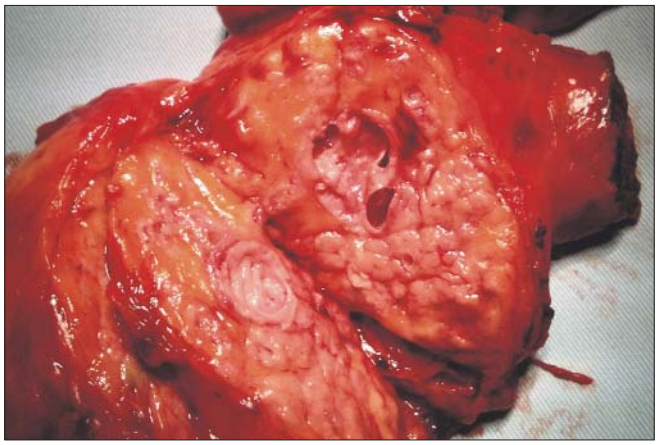

Figure 1. *IPMN in the head of the pancreas, misdiagnosed as a pseudocyst*

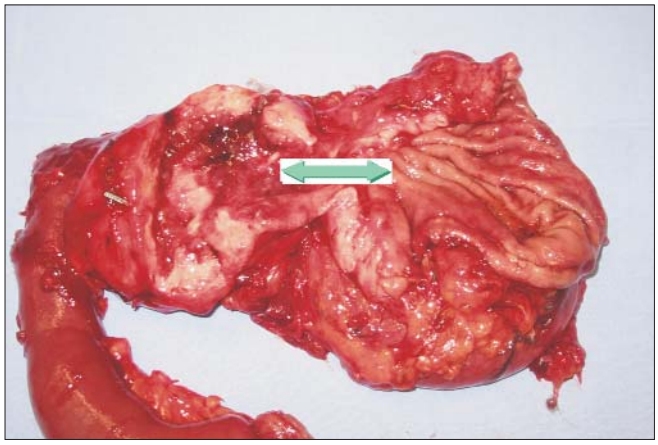

Figure 2. *'Cysto-gastrostomy' performed in a case of a large IPMN*

mainly with MRCP, even when it is multiple. However, the most important radiology imaging method is endoscopic ultrasonography. It not only detects septated mucinous tumours with correct size, localization and relation to the main duct, but also shows the so-called mural nodules. The presence of these nodules has a huge influence on the indication for surgery.

For surgery is not always indicated in case of IPMN. Whilst all forms of IPMN are considered precancerous pathologies, most of these cystic lesions are diagnosed in elderly patients, often without symptoms, with reasonable chance that they will never undergo malignant transformation.

IPMN can be classified in two groups: 'main-duct' (MD) and 'branch-duct' (BD) types. Invasive carcinoma can occur in both localizations, but they differ greatly in rates of malignancies. While the proportion of malignant MD-IPMNs is around 65%, the same rate does not exceed 25% in the BD-IPMN group.

Both risks are evidently high, and since IPMN has the greatest potential of becoming malignant amongst cystic tumours, it represents the most common indication for surgery for cystic lesions. Mucinous cystadenomas, cystadenocarcino-

mas and solid pseudopapillary neoplasms occur in only one fourth of the cases in our study cohort.

The former appellation of the intraductal papillary tumour was tubulovillous adenoma of the pancreatic duct, since it has similar characteristics as a colon lesion (*Fig. 3*). It is an appropriate analogy, for the sequence of an adenoma transforming into a carcinoma seems to be proven in IPMN as well. This progression is continuous and slow in nature so even benign forms are considered precancerous. The facts that IPMN can often be multifocal and that benign and invasive parts can be present at the same time in an adenoma make the situation even more complicated. The spectrum of malignancies varies from low grade dysplasia through high grade dysplasia and in situ carcinoma to invasive carcinoma.

Risk of malignant transformation depends not only on the localization but the phenotype of the expressed mucin as well. Four subgroups can be differentiated, such as gastric, intestinal, oncocytic and pancreato-biliary types. Histologically, branch-duct IPMN are always gastric type. Benign appearance of this form as an adenoma is relatively common and it rarely transforms into invasive carcinoma. Intestinal subtype IPMN arises almost exclusively from the main pancreatic duct and it has more potential (circa 30%) of becoming malignant.

An important difference between subtypes is that gastric (and pancreato-biliary) forms present as ductal carcinomas when malignant, while the invasive form of the intestinal subtype is the so-called colloid carcinoma with a remarkably higher 5-year survival (up to 55%) (*Fig. 4*). Presence of both K-ras and GNAS mutations are quite common in the intestinal form which can be of help in the diagnosis. Tumours of this subtype are relatively sizeable (reaching up to 50 mm in diameter) with severe dilation of the main duct (exceeding 10 mm).

All above circumstances should be taken into account when considering indication for surgery of an IPMN. Risk of progression of the tumour and mortality of the malignancy must never exceed the potential surgical morbidity and mortality rates. Due to uncertain outcomes and to lack of evidence, the matter is still under debate. Numerous guidelines have been introduced over the past decade, but all of them are based on consensus, with occasional contradictions. (2,3,5,6)

Unfortunately, available biomarkers can only verify tumour growth only after it has already become malignant and only without certain predictive value. Neither low grade nor high grade dysplastic precancerous pathologies can be diagnosed with accessible methods. An ideal biomarker would be a non-invasive test that requires blood or pancreas secretion sample, with high sensitivity for malignancy and ability to predict survival. Such a test would indicate clearly if the growth should be removed surgically.

Present biomarkers can be divided into four groups. Tumour markers, primarily CEA show no close correlation between their level and the malignant potential therefore they are not suitable to distinguish low grade from high grade dysplasia. Examination of mucin and cytokins might be useful. Increased MUC 2&4, IL1b, GM-CSF and PGE2 values seem to indicate high risk lesions. MicroRNA tests can also suggest

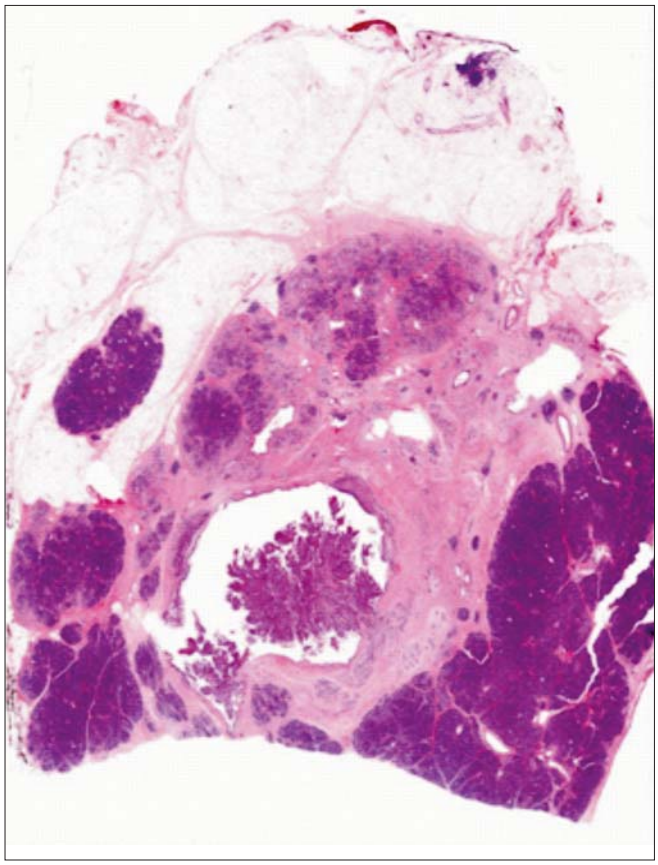

Figure 3. *Histological appearance of IPMN of the main pancreatic duct*

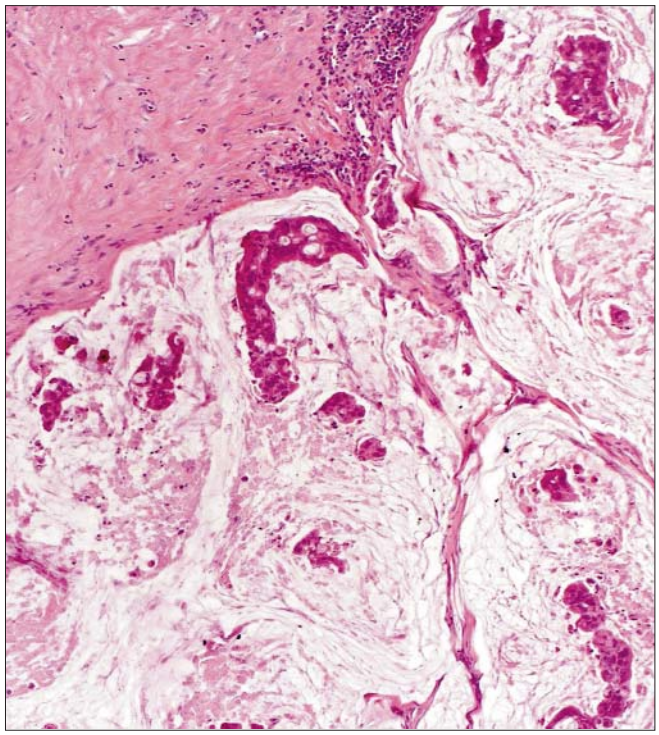

Figure 4. *Histological features of colloid carcinoma*

presence of high risk dysplasia and they are capable to distinguish IPMN from mucinous cystic tumours. Analysing K-ras, GNAS and LOH is also an option but without certain prediction of tumour invasion.

Nowadays, the primary indication for surgery is whether the tumour is main-duct or branch-duct type IPMN. Although mixed type lesions exist and it is not always possible to differentiate the above types prior to complete histological examination, the basic principle still remains that main-duct lesions should always be operated on due to the 65-70% chance of them becoming malignant.

Branch-duct lesions require a much more complicated decision. The need for surgical intervention depends on several circumstances, including tumour size, growth pattern, presence of solid, mural nodules, clinical symptoms, tumour marker levels and patient age. Regarding size, the risk of malignancy above the 30 mm limit is high enough to clearly indicate surgical removal of the lesion. BD-IPMN smaller than this size can be followed up if mural nodules are not present. Endoscopic ultrasound is the most suitable to verify mural nodules. In addition to this, rapidly growing cystic lesions tend to have a higher rate of being malignant. (7) 15-25% of cysts will gain size during follow up, one-third of them will eventually turn out to be invasive. Resection is therefore indicated if the size of the BD-IPMN increases by at least 5 mm in three years' time or by 2 mm over a single year period.

Presence of mural nodules always means increased risk. Once they are detected, surgery is appropriate even if the cystic lesion is smaller than 30 mm. High levels of CEA and CA 19-9 tumour markers, symptomatic lesions, icterus and recurrent episodes of acute pancreatitis are also indications for surgical resection. Advanced age is a relative contraindication for surgery. Two prospective studies have concluded that around 75-90% of deaths were not caused by pancreas disease in patients above 70 years who were observed for some years with BD-IPMN. (8, 9) Benefit from surgery is therefore very limited in elderly patients with co-morbidities.

30% of branch-duct IPMN are multifocal. This would suggest the need for total pancreatoduodenectomy, however it is only justified if the chance of familiar pancreas carcinoma is proven. Although, many issues still remain debated. As preoperative differential diagnosis of main-duct and branch-duct types is often difficult, and studies show that invasive carcinoma is present more frequently in the latter type, a more aggressive approach has appeared. A retrospective study carried out in Boston gives a relevant answer to this matter. (10) Indication for immediate resection occurred only in 20% of cases during the treatment of a total of 563 BD-IPMN patients. A further 20% underwent surgery in the 5-year follow up period. Not more than 10% of all these lesions turned out to be invasive carcinoma. Upon analysing these numbers it can easily be concluded that if all BD-IPMN patients underwent resection, the surgical mortality would exceed the expected mortality of the pancreas carcinoma itself.

There are other obvious ways to reduce risk. It is just in the case of BD-IPMN to perform an appropriate resection with parenchyma sparing. Both procedures, enucleating and central resection, are dependent on the exclusion of presence of either invasive carcinoma or dilation of main pancreatic duct. However, it must be noted that limited resections do not reduce the rate of complications, in fact, formation of a pancreatic fistula is most common after enucleation (*Fig. 5*). On the other hand, this risk is compensated by the avoidance of late exocrine and endocrine pancreas insufficiency and by lower surgical mortality.

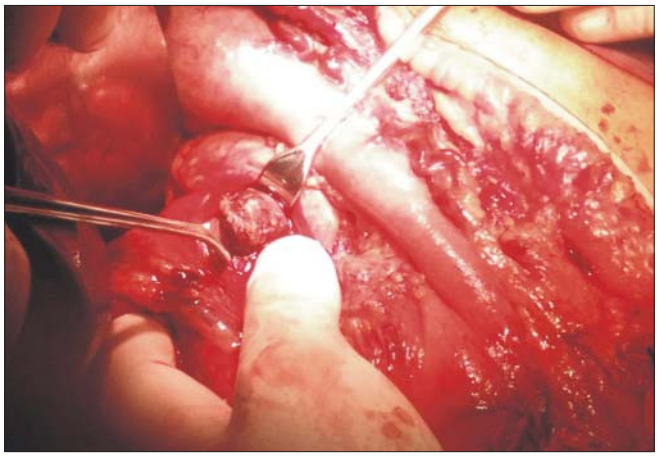

Figure 5. *Tumor enucleation from the head of the pancreas*

Since IPMN is multifocal and it spreads along ducts, with possible simultaneous presence of carcinoma and dysplasia, it is extremely difficult to determine appropriate surgical margins during resection. Intraoperative frozen section histologic evaluation is therefore required for all cases. What indicates the need for further resection? The most recently published meta-analysis shows that the risk of recurrent non-invasive IPMN is less than 10% even with positive surgical margins. (11) The same rate is more than 50% when invasive carcinoma is present, and even with clear margins there is 33% chance of recurrence. Up-to-date guidelines (2012-2013) therefore state that re-resection is indisputably necessary if invasive carcinoma or high grade dysplasia is detected in the surgical margin. Re-resection is also recommended in moderate grade dysplasia, but low grade dysplasia does not require further surgical intervention.

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