Review Article

Molecular and clinical patterns of local progression in the pancreatic remnant following resection of pancreatic intraductal papillary mucinous neoplasm (IPMN)

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Abstract: Intraductal papillary mucinous neoplasms (IPMN) are pancreatic cystic lesions that can progress to invasive carcinoma. Consensus guidelines indicate surgery for IPMN at high risk of malignant progression, as assessed by specific radiological and clinical criteria, whereas an active radiological surveillance is recommended for IPMN at low risk of malignancy. The management of IPMN is further complicated by the risk of developing a distinct new cyst or a ductal adenocarcinoma in the remnant pancreas, either synchronously or metachronously. Several studies therefore investigated local progression in the remnant pancreas following partial pancreatic resection for IPMN and whether an unstable epithelium at risk for malignant degeneration may exist. Understanding the biological mechanisms behind progression of IPMN will help in identifying patients that would benefit from the resection of the entire pancreas.

Keywords: Local progression; resected intraductal papillary mucinous neoplasm (resected IPMN)

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Introduction

Intraductal papillary mucinous neoplasms (IPMN) are pancreatic cystic lesions, characterized at pathology by dysplastic mucin-producing epithelium growing into the ductal system (1,2) and by neoplastic progression from low- to high-grade of dysplasia and to invasive carcinoma.

They are morphologically classified as main-duct (MD-IPMN), branch-duct IPMN (BD-IPMN) and mixed-type IPMN (MT-IPMN) based on the pancreatic duct involvement. Risk of harboring malignancy strongly correlates with the duct involvement with a high-risk disease [high-grade of dysplasia (HGD) and invasive carcinoma] being present in 61.6% of resected MD-IPMN and in 18.5% of resected BD-IPMN (3).

Based on histology and mucins expression, IPMN can be classified in four epithelial subtypes: gastric, intestinal, pancreatobiliary and oncocytic, each characterized by a different risk of malignant progression. Gastric type IPMN are usually low-grade lesions, whereas intestinal and pancreatobiliary type IPMN tend to be high-grade lesions and are often associated with invasive carcinoma (4,5).

Management of IPMN presents several clinical challenges. Over the years, consensus guidelines have defined the clinical and radiological criteria for the surgical *vs.* observational management of IPMN. According to the last set of guidelines, surgery is mandatory in case of 'high risk stigmata' (i.e., obstructive jaundice, enhancing mural nodules, main pancreatic duct >10 mm), whereas the presence of 'worrisome features' (i.e., pancreatitis, cyst >3 cm, thickened/enhancing cyst walls, main duct size 5–9 mm) warrant further specific studies. Considering that IPMN mostly occur in elderly patients and the annual rate of progression to HGD or invasive cancer is relatively low (1.4–6.9%), in absence of signs predictive of malignancy,

Table 1 Molecular analyses investigating patterns of local progression following partial pancreatic resection for IPMN

Author	Methods	Patterns of progression in the remnant pancreas
Matthaei *et al.* (7), 2012, *Ann Surg*	*KRAS* mutations and LOH analysis on chr 6q and 17p	Clonally independent multifocal BD-IPMN
Tamura *et al.* (8), 2014, *Ann Surg*	*KRAS*/*GNAS* mutations	Monoclonal skip progression for MD-IPMN
Pea *et al.* (9), 2017, *Ann Surg*	Targeted sequencing	High-grade independent IPMN; monoclonal skip lesions; direct progression from the resection margin
Omori *et al.* (10), 2019, *Gastroenterology*	Targeted sequencing and IHC of tumor suppressors	Sequential subtype, branch-off subtype, and *de novo* subtype

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

the management is therefore conservative (6). Moreover the management of IPMN is further complicated other peculiar characteristics of IPMN. The first is represented by the frequent finding of multifocal cystic lesions along the entire pancreas. The second is the increased risk of developing a distinct cyst or ductal adenocarcinoma (PDAC) in the remnant pancreas separate from the index cyst, either synchronously or metachronously. In this review we will focus on neoplastic progression in the remnant pancreas following pancreatic resection for IPMN. Using the term "local progression" we will therefore refer to the development of new lesions of unknown biological relatedness with the index cyst, whereas with the term "recurrence" we will refer to the reappearance of the same pancreatic disease in the remnant pancreas (locally) or with metastases (systemic).

Biological models of local progression

In recent years, progresses have been made in characterizing the genetic alterations underlying IPMN tumorogenesis. Next generation sequencing techniques have been used to demonstrate heterogeneity within the same cyst and to study molecular events underlying progression from low-grade lesions to invasive carcinoma. Comparing genomic alterations of multifocal and metachronous lesions allowed the development of spatial models of local progression across the entire pancreatic gland (*Table 1*).

Pea *et al.* (9) modelled tumor progression in the remnant pancreas by characterizing genetic alterations of pancreatic neoplasms in patients who underwent surgical resection for IPMN and had subsequent completion pancreatectomy for progressive disease in the remnant. In addition, in order to study the relation between synchronous but anatomically separated lesions, they also included in the study patients who underwent a resection for pancreatic ductal adenocarcinoma (PDAC) and had a concomitant IPMN.

Comparing molecular alterations, they assessed the relatedness of multifocal lesions and proposed 3 principal mechanisms responsible for local progression in the remnant pancreas.

Among patients with negative resection margins, clonally independent primary lesions were observed, some of them presenting HGD or invasive carcinoma. One explanation is that HGD IPMN could be the result of a diffusely unstable ductal epithelium prone to malignant degeneration, according to a widespread "field defect". This concept is further corroborated by evidences from clinical observations that concomitant PDAC presenting different genetic alterations can develop in different area from the index IPMN in patients undergoing resection and in those under surveillance for benign-appearing cysts (6). In order to investigate an inherited predisposition underlying the development of IPMN, Skaro *et al.* (11) recently evaluated germline variants from 315 patients with surgically resected IPMN. Among these, 3% presented germline mutations associated with pancreatic cancer and had a higher risk of developing concurrent invasive carcinoma. This is consistent with previous data on patients with familial pancreatic cancer, as more precursor lesions are observed in their pancreas than in patients without a family history (12,13).

Another less likely explanation for independent multifocal lesions is that the progressive lesion is the result of subclones of the original IPMN that were not used for the genetic analysis and seeded through the pancreatic ducts. This theory is in accordance to the already demonstrated polyclonality within the same cystic lesion (14).

When an IPMN was present at the resection margin, different outcomes were observed according to the grade of dysplasia at the margin. In case of HGD, the progressive

Table 2 Studies investigating clinical risk factor for progression after pancreatic resection for IPMN

Author	Type IPMN analysed	Oncological outcomes	Risk factors for local progression
Fujii *et al.* 2010, *Surgery* (20)	104 non-inv IPMN	Remnant pancreas, peritoneal surface	HGD at the margin
Miller *et al.* 2011, *HPB* (21)	243 IPMN (191 non-inv IPMN, 52 inv IPMN)	New radiologic IPMN, new PDAC	HGD at the margin
Leng *et al.* 2012, *Dig Surg* (22)	Review	New IPMN	HGD at the margin
Frankel *et al.* 2013, *HPB* (19)	192 non-inv IPMN	New IPMN, new PDAC	HGD at the margin
He *et al.* 2013, *J Am Coll Surg* (16)	130 non-inv IPMN	New radiologic IPMN	HGD in the primary, family history
Kang *et al.* 2014, *Ann Surg* (23)	366 IPMN (298 non-inv IPMN, 68 inv IPMN)	New IPMN, systemic recurrence	HGD in the primary, histotype
Pea *et al.* 2017, *Ann Surg* (9)	260 non-inv IPMN	High-grade disease (HGD, PDAC)	HGD in the primary, family history

IPMN, intraductal papillary mucinous neoplasm; inv IPMN, invasive IPMN; PDAC, pancreatic ductal adenocarcinoma.

lesion was genetically concordant, suggesting a direct extension of the IPMN in the remnant pancreas. When the margin lesion had LGD, the primary lesion, the lesion at the margin and the progressive lesion in the remnant were genetically independent. This is in line with data by Matthaei *et al.* (7) demonstrating that the majority of multifocal IPMN that arise in the branch ducts and harbor LGD in the lining epithelium are clonally independent.

In the study of Pea *et al.*, in one case with negative margins, a metachronous PDAC presented the same genetic alterations of the index IPMN. This is consistent with Tamura *et al.* (8) that analysed entire pancreatectomy specimens and described clonally related lesions separated by uninvolved pancreatic duct. Taken together, these data suggest that coexisting multisegmental IPMN involving different area of the main pancreatic duct may be generated by mutant clones spreading through the pancreatic ductal system (as recently demonstrated for PanIN lesions) (15).

Using a similar approach, a recent study by Omori *et al.* (10) analysed for genetic alterations the epithelium of non-invasive IPMN and the adjacent concurrent invasive carcinoma. By genetic mapping different area from the same IPMN they proposed 3 distinct models of neoplastic progression to invasive carcinoma. In the "sequential subtype", a progression from the coexisting IPMN with LGD to invasive carcinoma is documented with the invasive cancer sharing driver mutations with all concurrent IPMN. In the "branch-off subtype" the IPMN and the adjacent PDAC have identical *KRAS* but different *GNAS* mutations suggesting a clonal origin with later divergence. In "*de novo* subtype" no driver mutations are shared between PDAC and IPMN. When taken together with results from the previous studies, these data suggest complex relationships between multifocal lesions, whereas it still remains unclear the extent to which these issues may challenge IPMN clinical management.

Clinical patterns and predictors of local progression

Resected IPMNs have a good prognosis in terms of survival with a 10% and 27% range of progression rate in literature (16-19), however not all patients that recur will require an additional resection or will develop an invasive carcinoma. While the majority of patients with invasive carcinoma usually experience distant metastatic recurrences, only a minority of studies focused on the clinical patterns of progression following resection for non-invasive IPMN (*Table 2*). In the attempt of classifying these patterns, Pea *et al.* (9) described the radiological characteristics of progressive lesions arising in the remnant pancreas after resection of 260 non-invasive IPMN. "BD progression" was defined as a new BD-IPMN, an increase in size of an existing BD-IPMN, or development of a new solid component within an existing BD-IPMN; "MD progression", as an increasing dilatation of the main duct dilation and, "solid mass progression", as the development of a solid mass suspicious for PDAC in the remnant pancreas. In the second case, a stable dilatation of the main pancreatic duct over time was not considered progression but likely

postoperative stricture of the pancreatic anastomosis, as frequently observed after pancreaticoduodenectomy.

Some studies suggested that the risk of local progression is related to the overall grade of dysplasia within the primary IPMN. He *et al.* (16) analysed 130 resected non-invasive IPMN; among these, 43 (33%) patients present HGD at the final pathology and 22 (17%) developed imaging evidence of a new or progressive IPMN during postoperative follow-up. Among these, 5 patients developed an invasive carcinoma. Similarly, Pea *et al.* (9) described family history of pancreatic cancer and HGD of the primary tumor as independent risk factors for the development of a high-risk lesion in the remnant pancreas.

Kang *et al.* (23) analysed 366 patients with IPMN, including 68 with associated invasive carcinoma, and concluded that HGD in the primary tumor was positively correlated with recurrence, whereas a positive resection margin did not. MD IPMN had the higher rate of recurrence and, among histotypes, the intestinal and the pancreatobiliary presented a higher risk of progression in the remnant than the gastric and the oncocytic types (respectively 9.8%, 11.1% *vs.* 3.4% and 0%).

Several studies analyzed the significance of the margin status during pancreatic resection for IPMN through frozen section or at the definitive histology, not always with concordant results. While both IPMN and PanIN can be found at the resection margin, it is not clear when the pancreatic margin should be considered as "positive" and required additional pancreatic resection.

Frankel *et al.* (19) investigated 192 resected non-invasive IPMN and observed that any ductal dysplasia (including low grade IPMN and PanIN) at the final surgical was associated with progressive disease (31% with dysplasia at the margin *vs.* 13% without dysplasia). In this study, recurrence was defined as the development of new cysts in the remnant (31 patients), an IPMN requiring a re-resection (6 patients) and the development of a distinct pancreatic cancer (3 patients).

Fujii *et al.* (20) analyzed 103 patients resected for non-invasive IPMN. Those harbouring HGD presented an higher rate of local progression (22.7% *vs.* 4.9%), however with no differences in outcomes according to the resection margin status (respectively 10.7% of progression in patients with LGD at the margin *vs.* 7.8% in those with negative margins),

Miller *et al.* (21) analyzed 243 patients who underwent segmental resection for IPMN. Among 191 patients with non-invasive disease, 38 (20%) presented residual IPMN at the initial operation (8 had positive IPMN margins, 23 had further IPMN in the remnant and 7 presented both), one of them developed invasive cancer in the remnant. Among all patients, 31 (20%) developed a new radiographic lesion consistent with IPMN, 3 of them with an associated invasive cancer. Leng *et al.* (22) shows that the local recurrence rate in non-invasive IPMNs was 3.72% in patients with negative margin versus 9.56% in those with margins positive for any grade of dysplasia.

Conclusions

Over the next years, our understanding on the natural history of IPMN will expand further thanks to the longer follow-up time of patients under surveillance for benign cysts and of patients that underwent resection for IPMN. Local progression in the remnant pancreas following resection for IPMN represents a relevant clinical problem, in particular due to the increased risk of developing a new invasive carcinoma. Different biological mechanisms of neoplastic progression along the gland have been described, however further studies are needed to determine the clinical utility of distinguishing intraparenchymal spread from second primaries.

Overall, the future of IPMN management lies in integrating new molecular approaches with clinical and pathological findings to define specific subgroups that are likely to progress and that would benefit from the resection of the entire pancreas.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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