Intraductal Papillary Mucinous Neoplasia of the Pancreas – Pathologic Features and Molecular Markers – A Review

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ABSTRACT

Intraductal papillary mucinous neoplasm (IPMN) of the pancreas are pre neoplastic lesions defined by the World Health Organization as a grossly visible intraductal epithelial neoplasm that arises in the pancreatic ductal system, composed of mucin producing cells. The predisposing factor for their development as well as genetics are still largely unknown. Pathologists have a pivotal role in IPMN management since features like IPMN subtype, degree of atypia, margins status and presence or absence of an invasive component imply different patient management. In this article, we perform a review of the pathological features and molecular markers of IPMNs.

Key words: pancreas, intraductal papillary mucinous neoplasm, pathology, molecular markers

INTRODUCTION

The intraductal papillary mucinous neoplasm (IPMN) of the pancreas was first described in 1982 (1) and is defined by the World Health Organization (WHO) as a grossly visible intraductal epithelial neoplasm that arises in the pancreatic ductal system, composed of mucin-producing cells. IPMNs are rather common lesions, more prevalent in the older population (2,3). Some authors have described gender - and regional-specific differences, with IPMNs being more common in males in Eastern countries, while in Western countries there may be no difference in IPMN propensity between genders (4).

Currently, there are no well-established risk factors for IPMN development (2) but some have been linked it to genetic syndromes like familial adenomatous polyposis, Peutz-Jeghers and even Lynch syndrome (5,6).

The pathogenesis is not fully understood, but IPMNs often show progression to invasive adenocarcinoma via the adenoma-carcinoma sequence. Knowledge of the biological behavior is fundamental for a precise diagnosis and appropriate patient management (7).

Pathology evaluation is crucial for the correct characterization of the IPMNs in order to establish markers for patient risk stratification, both in pre and post-operative context.
**Importance of pathological evaluation**

Pancreatic cysts encompass a wide variety of neoplastic and non-neoplastic entities, the most prevalent being IPMNs, mucinous cystic neoplasm (MCN), and serous cystadenomas (8). The management of patients with pancreatic cysts is highly dependent on the subtype and the degree of dysplasia, which will define the risk of malignant progression and allow the proper patient selection for surgery (9). When the surgeon approaches a patient with pancreatic cystic lesions, clinical management starts with mucinous vs. non-mucinous cyst distinction and afterward with low versus high-risk definition (9,10). Currently, Fukuoka guidelines represent the gold standard in daily practice, with the definition of main duct and branch duct subtypes, and cysts with “worrisome features” (10). Non-neoplastic cysts do not require surgery, low-risk cysts can be managed by surveillance and in high-risk cysts surgery is the treatment of choice (9).

Radiological evaluations are not specific enough for malignancy, and the classification of branch duct type (pancreatic cysts bigger than 5 mm and with communication with the pancreatic main duct) and main duct type (segmental or diffuse dilation of the main pancreatic duct, > 5 mm, without causes for obstruction) IPMN has limited value (11). There is a higher risk of transformation to pancreatic ductal adenocarcinoma (PDAC) in main duct IPMN, and cystic fluid analysis associated with cytology is advised (7,9,10,12).

**Cytology approach and molecular markers**

**Cytology approach**

In order to develop an individualized approach of these patients, a precise and early diagnosis should be rendered. Endoscopic ultrasound (EUS) with contrast enhancement is a powerful tool for the differential diagnosis of pancreatic cystic lesions, especially when associated with fine-needle aspiration (FNA) (13). This is of upmost importance, since despite being stated in several consensuses reports (14–16) that proof of malignancy from the biopsy is not needed when clinical suspicion of malignancy is high (14,15,17), in up to 10% of the resected specimens the “pancreatic cancer” is another type of lesions such as chronic and autoimmune pancreatitis (18). Therefore, taking into consideration the morbimortality of pancreatic surgery, the correct differential diagnosis is fundamental for patient management.

In the diagnosis of cystic lesions of the pancreas, cytology has a pivotal role. EUS-FNA approach is safe, with high diagnostic accuracy with low seeding risk (usually the seeding track is removed with the surgical specimen), and can be performed on a pure cystic lesion or in the solid component in order to assess IPMN associated carcinoma (19).

Cytology is an accurate method to establish whether a cyst is mucinous or non-mucinous and to evaluate the degree of atypia (20). From a historical perspective, mucus-producing cystic neoplasms are considered rare; however, their incidence has been increasing, mainly due to increased detection by widespread use of imaging diagnostic tools (11,20).

Currently, the classification is based on the Papanicolaou Society of Cytopathology with the following categories: 1) nondiagnostic; 2) negative for malignancy; 3) atypical; 4) neoplastic; 5) suspicious for malignancy; and 6) malignant (21). In this cytological classification, IPMN with low or high-grade dysplasia is classified as “neoplastic”, and shows a very good correlation with risk of malignancy – up to 94.9% of specificity (21).

Thick and gelatinous mucous is the diagnostic hallmark of mucinous cystic lesions and easily perceived of evidenced by PAS-diastase stain (20); however, it is not related to lesion grade (22). The degree of atypia may be difficult to assess since the majority of the samples are pauci-cellular, but three-dimensional clusters with hyperchromasia are predictors of at least moderate dysplasia, while parachromatin clearing and necrosis foresee invasive carcinoma (20,22) (Fig. 1).

Ancillary studies may prove useful in assessing malignancy in IPMNs with the expression of insulin-like growth factor-II messenger ribonucleic acid-binding protein 3 (IMP3)(23) and P53 expression (24). The main differential diagnosis problem is posed by gastrointestinal contamination. While duodenal contamination is rather easy to discard (20), gastric contamination may prove to be more complicated; in this setting, immunostaining with B72.3 is a valuable ally revealing diffuse cytoplasmic staining in the neoplastic cells (25,26).

**Molecular markers**

EUS-FNA also represents a valuable tool for cyst fluid biochemical and molecular analysis (11,27,28). A fluid CEA level ≥ 192 ng/mL has been reported as being accurate for the classification of the cyst as mucinous (9,21). When the value of CEA is superior to 800 ng/mL with amylase level > 250 U/L the possibility of being a pseudocyst in unlikely (21). The combination of molecular studies, mainly GNAS and KRAS testing has been reported to have an 84% sensibility.
and 98% specificity for IMPN diagnosis (21).

GNAS is an oncogene located at the long arm of chromosome 20, and it represents an important tool for the IPMNs diagnosis since of all the markers available, GNAS mutations have been appointed as the most precise in the differential diagnosis and are found exclusively in IPMNs (7,12,28). The most common GNAS mutation occurs at codon 201 and it is found in up to 60% of IPMNs (28). Some studies have linked GNAS mutations to be more common in the intestinal subtype IPMN, and despite a more prevalent mutation rate of GNAS mutations in more advanced lesions, there has not been a solid association with concomitant PDAC and grade of dysplasia (7,9,28).

KRAS gene is an oncogene located on the short arm of chromosome 12 which has been reported to associate with IPMN with variable frequencies – 38-100% (28). KRAS mutation is considered to be an early event in IPMN’s malignant transformation (29). However, there is no significant association between KRAS mutations and the level of dysplasia (30). The possibility of discovering KRAS mutations in pancreatic juice, peripheral blood, and surgical specimens has turned this marker into a very promising diagnostic tool (28,31). Nevertheless, the testing of pancreatic juice must be interpreted with caution since KRAS mutations have been reported in mucin hypersecreting conditions as well as in chronic pancreatitis (28,32). Of note, KRAS mutations have been reported in the majority of pancreatobiliary IPMN subtypes (30).

In the same pathway, mutations in BRAF – a serine/threonine kinase located immediately downstream in the RAS signaling – have been described, but in lower frequencies – up to 3% (33). Despite their low frequency, the induced changes in the MAPK pathway, especially if associated with a RAS mutation, are expected to play an important role in IPMN malignant transformation, and potentially in an accelerated progression (28,33,34).

The role of the PI3K/Akt pathway has also been considered in IPMN pathogenesis. This pathway encompasses a large family of kinases with a role in cellular proliferation, differentiation, and survival, however, mutations in PI3K/Akt are only present in about 11% and seem to be a late event (28,33). P53 is an important tumor suppressor gene, located at chromosome 17 widely known as the guardian of the genome, playing key roles in cell cycle arrest, repair of DNA damage and regulation of senescence (35). In IPMN carcinogenesis, p53 mutations have been described as a late event, with inactivation in almost all invasive tumors associated with IPMN (28,36); when associated with loss of heterozygosity in p16, they are present in all invasive tumors (37). Mutations in the cyclin-dependent kinase inhibitor 2A/p16 (CDKN2A) gene which encodes p16, resulting in its loss of function
and accelerated cellular growth are thus a powerful tool for detecting malignant transformation (38,39). Therefore, additional testing for P53/PIK3CA/PTEN can have value in predicting advanced neoplasia (21,23,40).

Recently, several other genes have been implicated in IPMN carcinogenesis.

Hedgehog pathway is controlled by proteins responsible for the regulation of tissue and organ development, encompassing three major genes – desert hedgehog, Indian hedgehog, and Sonic Hedgehog (41); the latter is the best characterized and is reported in a higher percentage of invasive carcinomas and malignant IPMNs (42) and in the pancreatobiliary IPMN subtype (42). Interestingly, Sonic Hedgehog expression has been reported in higher expression in stromal cells in malignant IPMNs (42) and pancreatic juice from patients with IPMN but not in “normal” pancreatic juice, therefore having a major potential to distinguish between IPMN and chronic pancreatitis (43).

Mutations in telomerase reverse transcriptase (TERT) a gene on chromosome 5, are able to restore telomeric function, overcoming the so-called telomere crisis, and have been described in higher expression in malignant IPMNs (44). Serine/threonine kinase 11 (STK11) gene, tumor suppressor located at chromosome 19, has been associated with IPMN and PDAC, especially in patients with Peutz-Jeghers syndrome (45) and Brahma-related gene 1 (BRG1), encoded on chromosome 19 and associated with the SWI/SNF chromatin remodeling complex, has been reported in IPMNs, with higher frequencies in high-grade lesions (46).

In addition to mutations, gene methylation can also have a pivotal role in IPMN development and carcinogenesis (28). Hypermethylation is important in development (47), but aberrant hypermethylation and subsequent silencing of tumor suppressing genes is one of the major causes of carcinogenesis (48). In IPMN, hypermethylation is evident in more than 80% of cases (49) and more frequently in genes with well-characterized functions in tumor suppression – p16, APC, E-cadherin, MLH1, and MGMT (50). The number of methylated genes is higher in high-grade lesions (51) and more genes have been reported with a significant difference between lower and higher grade lesions such as TFPI-2, BNIP3, and PTCHD2, among others (28, S1,52). Henceforth the evaluation of methylated DNA in pancreatic juice could be useful for pre-surgical evaluation of non-invasive and invasive lesions (49).

MicroRNAs (miRNAs) are small molecules which functions as gene expression regulators. Their mechanism of action is by binding messenger RNA with its posterior degradation or translational inhibition (53). This effect may be important for cellular stability and proliferation control as well as apoptosis (53), and they can induce oncogenes expression or tumoral suppressor genes inhibition associated to pancreatic carcinogenesis (54–57). Of all miRNAs reported in the literature, miRNA-21, which inhibits PTEN and consequently activate the Akt signaling pathway, and miRNA-155, which represses a pro-apoptotic protein – (TP53INP1), are significantly upregulated in non-invasive IPMN and may achieve higher levels in patients with invasive component (55,58,59). The miRNA-21 has also been linked with chemotherapy resistance, worse overall survival and shorter disease-free survival, prompting it as a precious prognostic biomarker of worse prognosis (60-63). Conversely, miRNA-101 – a downregulator of EZH2 – has emerged as a good prognostic biomarker (58). Low levels of miRNA-101 have been associated with invasive tumors and higher levels with non-invasive IPMNs (56,57,63).

Finally, the members of the S100 protein have been implied in IPMN development and PDAC carcinogenesis (64,65). The members of this family have different cellular locations and besides functions in the Ca²⁺ signaling network, they have a role in cell cycle progression, proliferation and transcriptomic activity (66). Of the more than 100 members of this family, some have been associated with pancreatic carcinogenesis, especially the S100p and S100A4 (64,67). Both have higher levels in advanced IPMNs and in patients with invasive disease (28) and very interestingly S100P is measurable in pancreatic juice and its levels may allow discriminating neoplastic disease from its mimics, namely chronic pancreatitis (68,69).

The potential for this type of testing is increasing and nowadays they are possible in tissue and fluid cyst and feasible in most of Pathology Departments via Polymerase Chain Reaction (PCR) and Next Generation Sequencing (NGS) techniques.

The duodenal fluid has also been evaluated as a possible method for IPMN diagnosis and patient stratification since the duodenum is in direct contact with pancreatic juice, which contains the neoplastic cells. Since endoscopic retrograde pancreatography is not recommended by guidelines, the evaluation of duodenal fluid after secretin stimulation seems an easy and feasible approach – in the scenario GNAS mutations have been described in a consistent manner as in the pancreatic tissue (7). Finally, in the liquid biopsy era the analysis of circulating DNA is a promising method and some research has been made in that direction;
however, the low concordance in the resected specimens (56.3%) is still far away from the appropriate (7).

**Gross examination of surgical specimens**

The macroscopic examination usually shows a gross visible lesion, normally a dilation of the main duct or one or more cysts with communication to the pancreatic ductal system. A typical sign is mucin excretion from a patulous Ampulla of Vater (AFIP), which should raise suspicion for IPMN; this sign may be also appreciable in endoscopy examination (70,71).

The main pancreatic duct should be identified for lesion classification and its largest diameter should be recorded (72). Measuring the distance between IPMN and invasive carcinoma as well as sampling the tissue between the two components is highly recommended (73). The correct size of the lesion may prove of utmost importance in future risk assessment and would also allow correlating with the radiologic findings (72,74-76), however assessing the correct size of a cystic lesion may be challenging since cysts may rupture in surgical procedure or gross specimen manipulation (72). Recent recommendations suggest that if the cyst size on gross examination is inferior to the one reported on radiology, the latter should be used on the pathology report along with a commentary that justifies the use of that measure (72). In the case of unifocal but multicystic lesions, the overall size of the collections of locules and the dimension of the largest should be reported, while in multifocal lesions the largest focus dimension should be assessed (72).

IPMNs are usually cystic and any solid component should raise awareness for invasive carcinoma (77). The measurement of this component is also important since the may be overlooked or underestimated by radiology (72) and is fundamental for TNM classification (1).

The sampling of the lesions is fundamental for assessment IPMN grade of dysplasia and association with invasive carcinoma, therefore representing the major factor of prognosis in the patients with IPMN (1,72,78,79). An IPMN associated carcinoma may only be excluded after complete evaluation and sampling of the lesion and the pancreatic tissue in the vicinity (72) – which may harbor invasive and subtle carcinomas as well as neoplastic changes – a practice well implemented at our institution.

The macroscopic morphology of IPMN will depend on its location (77). Main duct type IPMNs are located in the main pancreatic duct. External pancreatic surface may be globous and after sectioning the main duct exhibit dilation and lumen filled with mucin and papillary/villous projections (80) (**Fig. 2** and **Fig. 3**). The majority of the main duct type IPMN are located in the head of the pancreas, but up to one third may be located in the body or tail. Due to main duct obstruction, the remaining pancreas usually shows obstructive chronic pancreatitis (77).

Branch duct type are found in the pancreatic secondary branches and have the appearance of a mucinous cyst (77) (**Fig. 4**). Since they usually do not induce obstruction, the remaining pancreas seems unremarkable81. This subtype is more common in the pancreatic head and uncinated process but up to 40% may be multifocal (77,80).

Mixed or combined type affects both the primary and secondary branches of the pancreatic ductal system (77). Clinical and biological characteristics are similar to the main duct type, so it is assumed the mixed type may represent an extension of the main duct type to the secondary ducts (82).

Unusual macroscopic features of IPMN have also
been described and include protrusion out of the ampulla (83), fistula to other organs (duodenum, small and large bowel, stomach) (84–87), mucin spilling to the peritoneum with pseudomyxoma peritoneum (88,89) and pancreatic calcification (90,91). Fistula formation was initially thought to be in association with malignant IPMN, but some cases of non-malignant IPMN with fistula have been reported (77).

Microscopic evaluation, classification and differential diagnosis

Microscopic examination, in the majority of situations start with a frozen section evaluation of the pancreatic surgical margin. Frozen examination of pancreatic surgical margin may be required by the surgeon, especially in patients with suspicion of invasive cancer; this evaluation can detect high-grade dysplasia or invasive tumor however it may miss discontinuous lesions that may be responsible for recurrence (11).

The main issue is the assessment of high-grade dysplasia/invasive carcinoma, since low-grade dysplasia does not require additional surgery; however, since low-grade PanINs are indistinguishable from low-grade IPMNs of the gastric type, no effort should be performed to discriminate between these entities and the focus should be on the evaluation of high-grade dysplasia/invasive carcinoma (10). High-grade dysplasia or invasive neoplasm should prompt for surgical resection extension, sometimes necessitating total pancreatectomy (11,92).

According to the recent WHO classification, IPMNs can be classified as pancreatic, gastric and intestinal subtypes (1). In the past, there was a fourth subtype, the oncocytic, nowadays reported as a different histological entity – intraductal oncocytic papillary neoplasm due to its unique architecture, lower association with PDAC and different molecular profile with ARHGAP26, ASXL1, EPHA8 and ERBB4 mutations instead of the more common mutations in IPMN described previously in this manuscript (1,8).

At histological evaluation, IPMNs correspond to the intraductal proliferation of mucin-producing cells of columnar morphology, which may be flat or forming papillae – microscopic or grossly evident (1). The grade of dysplasia should be granted according to the highest degree and classified as low-grade or high-grade, with the previously designed intermediate-grade dysplasia now included in the low-grade (73). Low-grade lesions exhibit mild to moderate cellular atypia, normally without mitoses and may not have papillary projections, while high-grade IPMNs display irregular and branching papillae with severe atypia, nuclear stratification, pleomorphism, prominent nucleoli and easily assessed mitotic activity (1,93).

After dysplasia assessment, one should classify the IPMN into one of the three major subtypes, according

Figure 3 - Surgical specimen of a main duct intraductal papillary mucinous neoplasm – marked dilation of the Wirsung channel – up to 6 cm in the periampullary region, with mucinous content and vegetations (black arrow)

Figure 4 - Gross examination of a branch-duct intraductal papillary mucinous neoplasm. On the left side a cyst accidentally opened during surgery, with smooth inner surface. On the right side, on cut section it is easily appreciable that the cyst does not have communication with the Wirsung (black arrows)
to the pattern of cellular differentiation – gastric, intestinal and pancreatobiliary (1). This is usually based on morphology and, especially on immunohistochemical profile determination – MUC1, MUC2, MUC5AC and MUC6; CDX2 and CK20 may have an additional role on the intestinal subtype (1,94). This classification is important since the three subtypes have different clinical presentations and, of utmost importance, different prognosis.

Gastric-type IPMNs are the most common and usually of branch ducts. The cells are tall and columnar with basal nucleus and mucinous cytoplasm, with an apical mucin cap, similar to the gastric foveolar epithelium (93) (Fig. 5). Scattered goblet cells may also be detected. Usually, gastric-type IPMN has a low-grade dysplasia but some cases may display high-grade dysplasia and invasive adenocarcinoma of conventional type (1,16). Gastric-type IPMN is less prone to develop an invasive component (93) at the phenotypic level, gastric type IPMNs usually have a diffuse expression of MUC5AC and MUC6, without expression of MUC1 and MUC2, although in the latter focal expression and on scattered cells is acceptable (77). As mimickers of gastric mucosa, in gastric type IPMNs expression should be more intense for MUC5AC in the superficial component and for MUC6 in the basal counterpart (95).

Intestinal-type IPMN is the second more common form, presenting typically in the main duct, with villous intestinal epithelium, forming papillae with enlarged and elongated nuclei and a variable amount of mucin, resembling intestinal mucosa (93) (Fig. 6). Intestinal-type IPMN commonly has high-grade dysplasia and when associated with invasive carcinoma it usually are of mucinous subtype with a better prognosis than conventional type (1,16,77). Mucin profiling should reveal diffuse expression of MUC2 and MUC5AC without expression for MUC1 and MUC6 (77).

Pancreatobiliary-type represents the less common subtype. Typically, it develops in the main duct and the papillae are more complex, branching arborizing and interconnected, lined by cuboid cells with amphiphilic cytoplasm, enlarged nucleus, and prominent nucleoli.
Figure 7 - Biliary type intraductal papillary mucinous neoplasm: complex and branching papillae are usually a feature (a, H&E 40x) and are lined by cuboidal to columnar cells with eosinophilic cytoplasm and marked nuclear atypia and hyperchromasia – high-grade dysplasia (b, H&E 200x)

(Fig. 7). Mucin is minimal (93). Most of the pancreato-biliary-type are high-grade lesions1. On this subtype, it is expected an expression of MUC1 and MUC5AC, without MUC2 and MUC6, although there can be focal expression for MUC6 (77).

The different immunoprofiles are summarized in Table 1.

Besides the role in subtyping the IPMNs, the expression of human mucins have been associated with invasive IPMNs with higher expression of MUC1 and MUC2 in advanced lesions (28,96,97). MUC4 expression, not present in normal pancreas, may reflect ErbB-2 activation and has also been linked to advanced and invasive IPMNs and could be a potential biomarker, especially since it can be detected in the cystic fluid (98–100).

Differential diagnosis

The main pathological differential diagnosis of IPMN is with MCN and pancreatic intraepithelial neoplasia (PanIN) (1). MCN does not have a communication with the pancreatic ductal system at gross examination, and are more common in pancreatic body/tail and in women (1,93). From an histological perspective, MCN is lined by mucinous columnar epithelium, underneath with an easily perceptive spindle cell stroma of ovarian type (1,93). On a cytological basis, the epithelium of IPMN and MCN are very similar and the ovarian stroma is necessary for the correct diagnosis – as cytology approaches cannot discern between these two entities (93). MCN is also linked to PDAC development (1). The main features useful for differential diagnosis are listed in Table 2.

IPMN and PanIN distinction may be particularly difficult. Size usually provides a very helpful tool since PanIN is usually under 0.5 cm and IPMNs are over 1 cm (73). However, small cysts with sizes between 0.5 and 1 cm present a borderline situation. Differentiation of cells may be an approach since almost all PanINs have gastric differentiation and IPMNs may exhibit intestinal and pancreatobiliary, but small gastric-type IPMNs may be virtually indistinguishable from PanINs (73). IPMNs would invariably start with smaller lesions that will progress with time and be characterized as IPMNs due to size; these lesions with 0.5-1 cm in size and gastric phenotype may be categorized under a descriptive lesion – intraductal low-grade neoplasm of gastric type 73 or use the term “incipient IPMN” (72). In this context, GNAS mutations have been reported in gastric-type IPMNs and absent in PanINs and can provide differential diagnosis (101,102).

Table 1 - Different immunoprofiles of the intraductal papillary mucinous neoplasm (IPMN) subtypes.

<table>
<thead>
<tr>
<th>IPMN subtype</th>
<th>CK7/CK19</th>
<th>MUC1/EMA</th>
<th>MUC2</th>
<th>MUC5AC</th>
<th>MUC6</th>
<th>CK20/CDX2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4/5</td>
<td>+</td>
</tr>
<tr>
<td>Intestinal</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Pancreatobiliary</td>
<td>+</td>
<td>+</td>
<td>-</td>
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Adapted from: WHO Classification of Tumours Editorial Board. Digestive system tumours. Lyon (France): International Agency for Research on Cancer, 2019
The remaining intraductal lesions of the pancreas have distinct morphological features and are easily identified: Pancreatic intraductal oncocytin papillary neoplasm, once a part of IPMN, has different molecular alterations and on a morphological level exhibits complex and arborizing papillae lined by oncocytic cells, sometimes in a cribriform pattern; the pancreatic intraductal tubulopapillary neoplasm has intratubular growth, but its pattern is predominantly tubular and without mucin production (1).

**Prognosis**

After the correct diagnosis is established, the other main characteristics that should be stated in the pathological report are staging and grading of the invasive component (if present) and evaluation of surgical margin status (72).

The surgical margin may be assessed in the frozen section, as stated before, or only after paraffin embedding (72,103). This is extremely important since it may stratify patients with a higher risk of disease progression/relapse, even in patients without non-invasive IPMNs (28,104). This so-called local progression, with increased risk of developing an invasive carcinoma, represents a clinical problem (104). The most well-established factor for higher risk of disease progression is high-grade dysplasia at the margin (104–109). Regarding negative surgical margins or low-grade dysplasia, several studies have proposed reasons for disease progression: monoclonal lesions, with high-grade dysplasia or invasive carcinoma, suggesting a diffuse and unstable ductal epithelium is the most accepted theory, especially in main duct IPMNs (110); while in the branch duct IPMNs clonally independent and multifocal lesions is the most probable mechanism (111). Irrespective of the origin of lesion in the remnant pancreas (recurrence or de novo), a close clinical follow-up is justified for patients with any degree of dysplasia at the surgical margin (73).

The mechanisms of IPMN progression to invasive carcinoma are not completely unveiled. In a recent discovery, genetic analysis by Omori et al. (112) established three distinct models of carcinogenesis: 1) a sequential model with low-grade, high-grade dysplasia and invasive carcinoma sequence, with driver mutations shared between IMPN and carcinoma; 2) a branch-off model, where IPMN and adjacent tumors share KRAS mutations but have different GNAS mutations; 3) a de novo model where no driver mutations where shared by IMPN and invasive carcinomas. The current clinical concept only provides evidence for the sequential subtype (16). The knowledge of two different pathways – the branch off and the de novo, which occur in about two-third of patients with IPMN after surgical resection – provides a major insight into the pathology of IPMNs that are multicentric/synchronous lesions and not a locoregional event and prompts for establishment of new surveillance guidelines (112).

**CONCLUSION**

In summary, IPMNs are complex neoplasms from the genetic standpoint. For their correct classification, it is of utmost importance the coordination of radiologic, gross examination and microscopic data evaluations. The pathologist plays a pivotal role in the approach of IPMNs and cytology with resort to ancillary markers, as well as molecular studies of cyst content may lead to a different patient management. Thus, it is critically important to correctly classify the IPMNs. Assessment of surgical margin status and invasive component should be mandatory. Due to the complexity of this entity, it is recommended that expert physicians manage IPMNs in reference centers.


Conflict of interest

All author declare that they have no conflict of interest.

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