

Intraductal Papillary Mucinous Neoplasm of the Pancreas; Up-to-Date

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Abstract

The intraductal papillary mucinous neoplasm (IPMN) is a proven precursory lesion of pancreatic cancer, maybe the most important. The pancreatic cancer is a pathology associated with high rates of mortality. The IPMN develops from the epithelial ductal pancreatic cells and it expresses as cystic dilation of the main pancreatic duct and/or its branches, being part of the differential diagnosis of the cystic pancreatic masses. The identification of "invasive" and high-grade dysplasia IPMN lesions is imperiously necessary for a correct therapeutic approach; the pancreatic complementary resection being indicated in all cases with high-grade dysplasia upon the surgical margins of frozen section examinations.

Keywords: Pancreatic cancer; Early detection; intraductal papillary mucinous neoplasm; IPMN

Introduction

Pancreatic cancer is the fourth cause of death by cancer in the developed countries, being one of the few cancers for which survival has not improved significantly during the last decades [1]. Even if pancreatic cancer is associated with high rates of mortality, a population-based screening approach is not suitable taking into account the low rates of occurrence of the pancreatic cancer in general population [2].

The occurrence of pancreatic cysts in the general population seems to be as high as 20% [3]. Together with the mucinous cystic neoplasia, invasive pancreatic neoplasia, and pancreatic intraepithelial neoplasia, the intraductal papillary mucinous neoplasia (IPMN) is one of the proved precursor lesions of the pancreatic cancer [4].

We intend to review in this paper the main aspects related to the IPMN occurrence, management and follow-up.

Definition

Described more than 30 years ago as a distinct tumor entity of mucinous cystic neoplasia or ductal adenocarcinoma [5], the IPMN is a cystic pancreatic neoplasia [6]. Its recognition increased significantly in the late years due to the advances in abdominal imaging [7,8]. Therefore, nowadays it seems that the IPMN lesions might represent up to 9.8% of the exocrine pancreatic neoplasia [9].

IPMNs develop from the epithelial ductal pancreatic cells and appear like cystic dilation of the main pancreatic duct and/or its branches [10]. Together with the mucinous cystic neoplasia, the IPMN is one of the two mucin-producing pancreatic neoplasms [11]. The IPMN lesions appear to be neoplastic precursors since, without treatment, aggressive clinical behavior of the tumor might develop following malignant transformation [12].

General Data

The IPMN is more frequently diagnosed in male than in female patients, especially in the seventh and eighth life decades [13]. The survival in patients diagnosed with IPMN is related to the form of neoplastic lesion, being substantially higher in patients with "non-invasive" than in those with "invasive" IPMNs; cases in which a 5-year disease specific survival of 46% was reported [14]. The occurrence of IPMN seem to be associated with some clinical conditions such as

antecedents of diabetes (especially when insulin dependent), chronic pancreatitis or pancreatic ductal adenocarcinoma [15].

Morphology

The IPMN are classified into three types: main duct IPMN, branch type IPMN, and mixed type IPMN, according to criteria stated upon imaging studies and/or histology [16]. The main duct IPMN represents segmental or focal dilatation of the main pancreatic duct with more than 5 mm diameter. The cystic pancreatic lesions with diameters between 5 and 9 mm are considered "worrisome features" while those having more than 9 mm are taken into account as "high risk stigmata" [17]. Branch duct IPMN represents pancreatic cyst with more than 5 mm diameter that communicate with the main pancreatic duct. Mixed types associate both main and branch duct IPMN criteria [17]. For the presence of two or more cystic lesions in the pancreatic parenchyma that have communication with the main pancreatic duct, the term multifocal branch duct IPMN was proposed [18].

According to the degree of differentiation, the IPMN lesions are classified as low-grade dysplasia in the case of adenoma, intermediate-grade of dysplasia in borderline lesions, respectively high-grade dysplasia [14].

In the case of IPMN, the benign lesions are those with low grade of dysplasia, the intraductal papillary mucinous adenoma. The intraductal mucinous tumors with moderate dysplasia are considered borderline tumors and the ones with associated carcinoma, regardless the invasive or non-invasive characters, are invasive malignant pancreatic tumors [9].

The duct cells proliferation as well as the mucin secretion leads to the pancreatic duct dilation, the specific imagistic characteristic

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of the IPMN [2]. One of the main IPMN's features is the production of mucin, IPMN being therefore classified as one of the mucinous pancreatic neoplasia. The mucins, either transmembranary or secreted, are contributors to the epithelial mucous barriers and are also involved in inflammation and cancer development, and are playing a role in cell growth and cell survival [20].

Tumoral Markers

Mucin type 1 (MUC1), a transmembranary mucin, is considered a marker of an "aggressive" pathway of tumor development; MUC 1 inhibits the cell-cell as well as the cell-stroma interactions, therefore facilitating the tumor invasiveness. Also, MUC1 interferes with the immune resistance of the neoplastic cells. On the contrary, the mucin type 2 (MUC2), one of the secreted mucins, interferes the gel formation and seem to characterize the "indolent", benign pathway of the pancreatic carcinogenesis [21].

There have been characterized four different histopathological varieties of the IPMN: gastric, intestinal, pancreaticobiliary, and oncocyctic type [22,23]. Their classification is made by immunohistochemical examination taking also into consideration the mucin expression. The gastric IPMN has in general a uniform structure and is responsible for low-grade dysplasia, expressing mainly mucin type 5 (MUC5). The intestinal IPMN generally presents MUC2 expression. The pancreaticobiliary IPMN is the most aggressive; it expresses MUC1 and is accountable with a high-degree dysplasia. The up-regulation of MUC1 is otherwise a late pathogenic event in the pancreatic cancers [17].

Besides mucins, there are also other biological markers, like IL1 β , PGE2, KRAS, GNAS), and the 9 miRNA, that were included into an extended panel which might lead to determining the biological signature of the tumor mass [24].

The fluid contained in the pancreatic cyst was analyzed for tumor markers such as the carcinoembryonic antigen (CEA), CA 19-9, CA 72-4, CA 125, and CA 15-3. Among all these markers, the CEA concentration in the cyst fluid seems to be the most accurate diagnosis test for differentiating the neoplastic mucinous lesions from the non-mucinous pancreatic cystic lesions [25].

Imaging Diagnosis

The main imaging features of the cystic pancreatic tumors are: serous cystadenoma and mucinous cystadenoma. The serous cystadenoma are generally less than 2 cm diameter, lobulated, with no communications with the main duct, but with central calcifications. The mucinous cystadenoma have frequently more than 2 cm and are smooth, well encapsulated, without lobulated contours. The communications with the main duct are absent in mucinous cystadenoma and mural nodules might be seen. When present, the calcifications have peripheral distribution, not central. The IPMN might have either a lobulated or a smooth aspect, mural nodules might be present, but the calcifications are atypical [26]. The pancreatic cysts with more than 3 cm in diameter have to be explored by EUS after the usual CT/ MRI approach [17].

The endoscopic ultrasonography (EUS) might play an important role in IPMN evaluation because it also allows the sampling of the cystic fluid. The EUS provides useful information on the cystic wall aspects, presence of mural nodules or septa [27].

Management

There aren't any "evidence based" guidelines, but consensus on the IPMN management at the level of current published evidence is weak, generally based on retrospective and uncontrolled studies [17]. In the 2012 consensus, the indications for resection are more conservative, the branch duct IPMN more than 3 cm without presence of "high

risk stigmata" could benefit from follow-up, without immediate surgical intervention. Limited resection without lymphadenectomy or splenectomy was proposed when there was no suspicion of malignancy, whereas pancreatectomy with standard lymph nodes dissection was recommended for invasive or non-invasive IPMN or MCN [17].

In the case of the main duct IPMN and mixed type IPMN, pancreatic resection is indicated taking into consideration the high risk of malignancy. Based on the preoperative imaging exams results, the type of the pancreatic resection should be established. If the CT/ MRI examination does not reveal malignancy in the tail region, the pancreaticoduodenectomy is the recommended intervention. During the surgical intervention, the frozen section examination of the pancreatic margins is necessary to decide the follow-up. In the case of high-grade dysplasia, the extension of the pancreatic resection is indicated. The low grade dysplasia does not impose extending resection while in the case of intermediate grade of dysplasia the decision is more difficult, other patients' characteristics should be considered as well [17].

The risk of diabetes mellitus (neither incidence nor prevalence) seems not to differ between patients resected for IPMN when there is no high grade dysplasia and those being assigned to follow-up [28].

In selected cases, observation only, without pancreatic resection could be taken in consideration. By having newer and more accurate diagnostic tools, the indication and timing of surgical intervention became more selective nowadays [29].

Prognosis

Yogi T et al found among 153 patients diagnosed with IPMN, low/ intermediate grade dysplasia in 54.9%, high grade dysplasia in 22.2%, stromal invasion <5 mm (T1a) in 4.6%, and invasive intraductal papillary mucinous carcinoma in 18.3%. The median follow-up of this cohort was 46,4 months and the recurrence rates observed were 6.0%, 5.9%, 42.9%, respectively as high as 57.1% [30].

The small IPMN associated invasive carcinoma represents approximately 25% of the all resected IPMN - associated invasive carcinoma. Among these, 57% are tubular adenocarcinoma and 29% colloid adenocarcinoma. The overall recurrence rate observed is 24% with a median time of recurrence of 16 months [31].

Kwon JH et al described in 337 patients with branch type IPMN: 37 patients with multifocal branch duct type IPMN, 22 patients with remnant multifocal branch IPMN (1 central pancreatectomy, 14 distal pancreatectomy, 7 standard pylorus-preserving pancreaticoduodenectomy). The malignancy was suspected based upon the following criteria: diffuse dilation of the main pancreatic duct with a diameter larger than 10 mm, tumor diameter more than 3 cm, significant pain or abdominal discomfort. Within a period of 40 months of follow-up, only one patient with associated invasive carcinoma died [18].

Recurrence and Follow-up

Tumor location, mural nodule size, presence of invasive cancer, lymph node metastasis, IPMN persistence in the pancreas remnant, and main duct dilation after surgery were identified as risk factors for tumor recurrence after surgery [30,31]. Moreover, Nara S et al, on multivariate analysis models, identified the presence of lymph node metastasis, serosa invasion, and a high level of serum carbohydrate antigen 19-9 as predictive factors of recurrence after intraductal papillary mucinous carcinoma resection [32].

The recurrence after the noninvasive IPMN could be due to the residual dysplastic cells in the surgical margins, presence of multicentric

tumors with asynchronous lesions overlooked in the pancreas remnant or metachronous lesions in the pancreas remnant [33].

Because the IPMN is a lesion that usually is accompanied by a slow-growing pattern, the follow-up should be probably maintained on long-term. Some authors reported no mortality on a period of 4-years follow-up after resection [34] and others a 94% survival-rate after a 5-years follow-up period [35].

Conclusion

The IPMN is an increasingly documented entity in the last decades, a cystic pancreatic mass characterized by mucin production. The type of the produced mucin could be a marker of the tumor mass development pathway, “aggressive” when associated with MUC1 production and “indolent” in the case of MUC2 production. The surgical management is decided by the expressed tumor type, the pancreatic resection being the only solution in high-grade dysplasia. The global survival in patients with low-grade dysplasia IPMN is optimistic, but long-term follow-up should be indicated in these patients if considering the slow-growing pattern of the IPMN.

Conflict of interests

The authors have no conflicts of interest to declare.

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