The Clinical Management of Main Duct Intraductal Papillary Mucinous Neoplasm of the Pancreas

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Keywords

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Abstract

Background: Intraductal papillary mucinous neoplasms (IPMNs) of the pancreas comprise a heterogeneous group of intraductal mucin-producing neoplasms representing a typical adenoma-to-carcinoma sequence. The involvement of the main pancreatic duct (MPD) is a feature of paramount importance, directly related to a more aggressive biology and a higher malignancy rate. **Method:** We review and discuss the clinical management of IPMNs with a MPD involvement, recalling the different consensus guidelines and addressing recent controversies in literature, presenting the current clinical practice in Verona Pancreas Institute. **Results:** All the aspects of surgical management were discussed, from the indication for surgery to the intraoperative management and the follow-up strategies. **Conclusion:** The management of presumed IPMNs involving the MPD at our Institution is in line with the International Association of Pancreatology 2012 guidelines, revised in 2016. Surgical resection proposed

should achieve the complete removal of the tumor with negative margins. Despite a good prognosis in terms of survival of overall resected main duct intraductal papillary mucinous neoplasms, follow-up should not be discontinued.

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Introduction

Intraductal papillary mucinous neoplasms (IPMNs) were formally described for the first time by Ohashi in 1982, with the finding of a “mucous secreting pancreatic cancer” [1]. In 1994, a group of pathological entities that were previously reported under different denominations in the literature were finally embraced in the term “IPMN” [2].

Since these first reports 30 years ago, it became clear that IPMNs of the pancreas represent a heterogeneous group of lesions, diagnosed with an increasing frequency due to the extensive use of cross-sectional imaging [3, 4]. Still it remains difficult to estimate their actual preva-

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Fig. 1. IPMN involving the main pancreatic duct (MPD): CT view (a); magnetic resonance cholangiopancreatography (MRCP) view (b); specimen for final pathology (c).

lence, since they are often asymptomatic and incidentally discovered [5].

A lot has been learned about the nature and behavior of these neoplasms, and increasing experience and clinical evidences have eventually led to the introduction of algorithms of management, like the International Association of Pancreatology (IAP) International Guidelines [6–8]. However, many of the diagnostic criteria and management protocols remain challenging to apply and some are extremely controversial.

Definition

IPMNs are defined as preinvasive, intraepithelial, mucin-producing neoplasms that grow within the ducts of the pancreas [6–9]. In order to distinguish IPMNs from incidental microcysts and pancreatic intraepithelial neoplasms, they were required to be more than 1 cm in diameter according to the World Health Organization 2010 (WHO–2010) classification [10].

Based on the location of the disease along the pancreatic ducts, IPMNs are further classified morphologically into 3 discrete entities: IPMNs involving only the side branches of the ductal system (BD-IPMN) and IPMN involving the main pancreatic duct (MPD; Fig. 1), exclusively (main duct intraductal papillary mucinous neoplasm [MD-IPMN]) or together with side branches (Mixed type IPMN). Of note, the present article is aimed to exclusively review and discuss the clinical management of IPMNs with an MPD involvement.

Histologic Classification

IPMNs represent a typical adenoma-to-carcinoma sequence, as they encompass a wide spectrum of dysplastic changes. Such spectrum is actually categorized as “low-grade dysplasia – high-grade dysplasia – invasive carcinoma” per the 2015 Baltimore Consensus (abandoning the previously adopted term of “intermediate dysplasia”) [11].

IPMN have been further classified into 4 different cytological types, namely, the gastric, intestinal, pancreatobiliary, and oncocytic. These types are characterized by different histologic features, specific mucin expression, and different genetic drivers. Eventually, IPMNs can progress to invasive carcinoma through 3 different patterns: ductal/tubular, colloid/muco-nodular, and oncocytic [12–15].

The heterogeneity of the disease is well represented by the different behavior and likelihood of malignancy of these subtypes. Of note, different epithelial types and invasive components can coexist in the same IPMN. MD-IPMNs are frequently associated with an epithelium of the intestinal-type, and harbor a high likelihood of malignant progression. However, when carcinoma occurs, this is most likely of the biologically less aggressive colloid type [12, 13]. The gastric epithelial subtype, which is less common for MD-IPMN, has a lower likelihood of progression into invasive cancer. However, once this is present, it is of the ductal/tubular type, an aggressive entity with a high rate of local invasion and nodal metastasis and a poorer prognosis (similar to that of ductal adenocarcinoma) [14, 15].

The pancreatobiliary and the oncocytic subtypes are less common: the former is associated with the highest rate of invasion and transformation into ductal/tubular carcinoma; the second is more indolent even if there is a relevant rate of recurrence after surgical resection [16].

MD-IPMN vs. MPD Dilatation

While most of the first reported cases of IPMNs involved the MPD, with time it became clear that the disease could also originate in the side branches of the pancreatic ductal system. This is a distinction of paramount importance, since the site of involvement revealed to be directly related to the biology of the disease and malignancy rate.

MPD dilation in IPMNs is often the resultant of the mucous produced by the underneath neoplastic process, which is located in the duct walls. Such dilation is therefore only an indirect sign of the disease, representing a diagnostic dilemma for the clinicians once resulting at tomographic imaging. MPD dilations represent indeed a broad spectrum of conditions, from IPMNs to other benign (ductal hypertension caused by mucin hypersecretion/mucin plugs, and obstructive chronic pancreatitis) as well as malignant entities (solid tumors with retrograde MPD dilation). Moreover, solid components like mural nodes can often be challenging to identify, as mucin plugs can frequently mimic them.

An MPD involvement by IPMN is associated with a more aggressive biology. In large surgical series, MD-IPMNs have been reported to harbor malignancy in more than 60% of the cases, with rates of invasive cancer of more than 40%. Of note, BD-IPMNs have a more indolent nature, with a malignancy rate in the same series of around 25% and of invasive cancer of 16% [7, 17]. It is important to underline that these notions are mainly driven from retrospective analysis of surgical series, generating a significant intrinsic bias. The actual malignancy risk for IPMNs is still unknown, as literature is still lacking reliable data regarding prospectively observed lesions in the long term.

Historically, mixed-type IPMNs have been categorized and treated like MD-IPMN, assuming a similar risk of malignancy due to the involvement of the MPD. However, in 2014, a paper from the Heidelberg group reported a rate of histologic MPD involvement of 29% in resected presumed BD-IPMN [18]. Moreover, the MGH group demonstrated that a minimal involvement of the MPD by the IPMN does not carry the same malignant potential as a true MD-IPMN. In fact, minimal MPD involvement was frequently of the gastric type and the risk of high grade dysplasia and invasive carcinoma was only 11 and 6%, respectively, when compared to that of BD-IPMNs [19]. As a result, not all mixed type IPMNs should be categorized together, as the actual involvement of the MPD carries a different risk of malignancy [17].

Finally, regardless of the extent of the ductal system involvement, IPMNs tend to be multifocal. This has been defined as a “field defect” of the entire gland. The risk of developing a synchronous or metachronous IPMN is therefore significantly higher, as well as that of a metachronous ductal adenocarcinoma that must be distinguished from an invasive component arising from the IPMN [20, 21].

The Clinical Management of MD-IPMN

Indications for Surgery

The Clinical management of MD-IPMNs is compound and constantly evolving. Several guidelines have been published in this regard to orientate the clinical practice. According to the IAP Fukuoka 2012 guidelines, which has been recently revised, surgical resection is recommended for all MD IPMNs with an MPD greater than 10 mm in diameter, or presenting with other “high risk stigmata” (HR) like an enhancing solid component or related jaundice [7, 8]. A dilation of MPD between 5 and

Fig. 2. Clinical algorithm for the management of IPMNs according to 2016 revised IAP consensus guidelines [8]. ^a Pancreatitis may be an indication for surgery for relief of symptoms. ^b Differential diagnosis includes mucin. Mucin can move with change in patient position, may be dislodged on cyst lavage, and does not have Dop-

pler flow. Features of true tumor nodule include lack of mobility, presence of Doppler flow, and FNA of nodule showing tumor tissue. ^c Presence of any one of thickened walls, intraductal mucin, or mural nodules is suggestive of main duct involvement. In their absence, main duct involvement is inconclusive.

9 mm is considered a “worrisome feature,” with no recommendation to immediate resection but requiring further evaluation with endoscopic ultrasound (EUS) [7, 8]. In 2013, the European expert consensus statement on cystic neoplasm was published, confirming the IAP recommendations for surgery in all IPMN involving the MPD of more than 1 cm in diameter, the presence of mural nodes, or related symptoms [22] (Fig. 2). In 2015, the American Gastroenterology Association (AGA)’s Clinical Practice Guideline Committee released their guidelines on the management of asymptomatic neoplastic pancreatic cysts. Surgery was indicated for an asymptomatic patient only if a cyst has 2 of the 3 “concerning features” (presence of nodule, size >3 cm, or duct dilation) and EUS shows malignancy at the fine needle aspiration [23]. This last extremely conservative approach is based on the analysis of a database of 3.5 million estimated cysts in the general population, which revealed

only 1,137 (0.032%) cases of “mucinous pancreatic adenocarcinoma.” This would suggest an actual risk of cancer considerably lower than previously estimated, even if controversies have emerged regarding the accuracy of provided data.

According to all current guidelines, surgery is warranted in all cases of IPMNs involving the MPD, but there’s still no consensus regarding the clinical management once MPD dilation is diagnosed. In the absence of other “HR,” MPD dilatation alone is characterized by a considerable risk of misdiagnosis and possible overtreatment. For these reasons, some authors suggested radiologic surveillance in asymptomatic patients with “worrisome” MPD dilatation (5–9 mm) and lacking other HR [24]. Conversely, after observing a “risk” of malignancy of 59% among resected IPMNs with an MPD involvement between 5 and 9 mm and in the lack of statistical correlations between MPD diameter and clinical and/or

IPMN features, Hackert et al. [25] suggested that the threshold for surgery to all MPD dilations above 5 mm be lowered.

A word of caution must be mentioned in this regard. As stated before, the clear majority of studies defining the malignancy risk for IPMNs are derived from surgical series. By definition, such studies fail to evaluate the actual incidence of malignancy in the overall population of individuals harboring MPD dilatation. In 2016, a multicentric study has analyzed the mid-term outcomes and predictors of survival in non-operated patients with presumed IPMNs. The authors found that patients with IPMNs with worrisome features had a 5-year disease-specific survival of 96%, suggesting that a conservative management is appropriate in these cases.

On the other hand, the presence of HR was associated with a 40% risk of IPMN-related death, reinforcing the policy of surgical resection in fit patients [26].

The management of presumed IPMNs involving the MPD at our Institution is in line with the IAP 2012 guidelines, revised in 2016. In detail, the sole “absolute” criterion for surgery is lesion-related obstructive jaundice, a condition that is highly suggestive of cancerization. Moreover, we recommend surgery for all fit patients presenting with MPD dilation >1 cm or an enhancing solid component. Each case should be carefully evaluated with the patient after adequate counseling, stressing the role played by general clinical conditions, age, and comorbidities. Patients presenting “HR” undergo a close surveillance with MRI with magnetic resonance cholangiopancreatography, oncological markers, and EUS when indicated. During follow-up, a progressively increasing MPD dilation, the appearance of a suspect mural node, and an increased serum level of CA 19-9 are solid criteria to reconsider a surgical approach.

Intraoperative Management

Since the preoperative selection is aimed to detect lesions harboring malignancy, the surgical resection proposed should achieve the complete removal of the tumor with negative margins. Consequently, parenchyma-sparing pancreatectomy, like enucleation, uncinate resection, and middle pancreatectomy, does not represent safe policies for MD-IPMNs, as the disease is presumed to be malignant. On the other hand, upfront total pancreatectomy represents a matter of debate, in particular for younger patients who would undergo a lifelong follow-up [27], given their higher cumulative lifetime risk of malignancy development. In these patients, the attempt to preserve parenchyma could lead to a lower risk of exocrine/endo-

crine insufficiency, postponing the long-term effects of DM. The acceptable risk of recurrence and related death seems preferable to the morbidity and mortality of a total pancreatectomy. Moreover, appropriate lymphadenectomy should always be associated with resection [28]. Nodal staging has shown to have a prognostic value, for both survival and recurrence. In this regard, adjuvant therapies should be proposed at least in N+ patients [29].

As preoperative imaging fails to determine the exact extension of the disease in MD IPMN, an important role in the decision making is played by the intraoperative frozen section of the resection margin [30]. The literature states that a “free margin” should be achieved; however, no consensus has been reached in defining the absence of a positive margin [31]. Moreover, the intraoperative histological interpretation can be difficult as well because of artifacts, small focuses of dysplasia, and challenging distinction in the grade of dysplasia. Furthermore, the IPMN might present with skip lesions in the remnant pancreas [28, 32, 33]. The IAP guidelines suggest that when adenoma (meaning low-grade dysplasia) is present at the resection margin, no further resection is required because the risk of progression to cancer or local recurrence is minimal [34]. Conversely, high-grade dysplasia, as well as invasive carcinoma, requires additional resection, up to a total pancreatectomy. In MD-IPMNs, the frozen-section margin analysis is of particular importance, as the dilatation of the MPD might be either IPMN-related or due to the obstruction [32].

Another important aspect is represented by the finding of inflamed ducts with a “denuded epithelium,” which makes the pathologist unable to assess the presence of neoplasia [28]. Despite this specific event, the intraoperative assessment of the resection margin is reliable at high-volume centers, being confirmed at final pathology in most of the cases [35]. However, once unexpected malignancy is found at final pathology, surgical re-exploration should be taken into consideration together with other factors that determine the choice of extending a partial surgical resection, like age, general clinical conditions, preoperative diabetes, family history, and patient’s choice.

Postoperative Follow-Up Strategies

The length, the frequency, and the methods of surveillance for resected IPMN still represent a matter of debate in the surgical community. Tumor recurrence can be classified as local, regional, or distant. Overall, resected IPMNs have a good prognosis in terms of survival, and the recurrence rate reported in the literature ranges from 10 to 27% [36–38].

The recurrence pattern for resected benign IPMNs may occur because of synchronous, low-risk lesions left behind, the development of metachronous lesions in the healthy remnant gland, or lesions arising from tissue at the surgical margin. Isolated regional or distant metastases in patients with noninvasive resected IPMN should be referred to a new disease arising from the remnant pancreas, probably due to an undetected concomitant PDAC [38–40].

Considering resected noninvasive IPMNs, the prognosis is reported to be excellent with a 5 years survival rate ranging from 77 to 100% according to different series [35, 36, 38]. The risk of recurrence is lower than 10% and in median 4 years after surgery [38].

With regards to resected invasive IPMNs, these are more likely to recur with regional or distant metastases than in the pancreatic remnant, particularly in case of positive lymph nodes [29, 35, 38]. The disease-free survival of resected invasive MD-IPMN is reported to be of 79 and 62% at 2 and 5 years [17], suggesting that postoperative surveillance should follow the scheme of ductal adenocarcinoma. With regards to IPMN-invasive types, tubular cancers have higher risk to have lymph node involvement [13, 38], whereas oncocytes tend to recur

many years after pancreatectomy with good long-term prognosis even in case of surgical re-exploration [16]. In this regard, the discontinuation of follow-up after 5 years proposed by the AGA guidelines in 2015 [23] might lead to the underestimation of tumor recurrence [41].

The follow-up of resected IPMNs present several peculiar aspects. In case of resected MD-IPMN, the dilatation of the MPD in the remnant pancreas might be of difficult interpretation, as it occurs almost invariably after a pancreaticoduodenectomy. The surveillance strategy should therefore focus on the progressive changes of MPD itself, such as a progressive widening of the diameter and the appearance of solid component, correlated with the value of CA19-9 serum level and the clinical status.

There are currently no formal recommendations regarding the use of adjuvant therapy in patients with invasive IPMN, but some recent studies have suggested that these patients could benefit from it compared with surgery alone [42].

Disclosure Statement

The authors declare that they have no conflicts of interest to disclose.

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