

# Natural History and Management of Intraductal Papillary Mucinous Neoplasms: Current Evidence

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## Keywords

Intraductal papillary mucinous neoplasm · IPMN · Pancreas · Natural history · Malignant transformation · Cancerogenesis

## Summary

**Background:** With the use of modern cross-sectional abdominal imaging modalities, an increasing number of cystic pancreatic lesions are identified incidentally. Although there is no pathological diagnosis available in most cases, it is believed that the majority of these lesions display small branch-duct intraductal papillary mucinous neoplasms (BD-IPMNs) of the pancreas. Even though a number of large clinical series have been published, many uncertainties remain with regard to this entity of mucinous cystic neoplasms. **Methods:** Systematic literature review. **Results:** Main-duct (MD) and mixed-type IPMNs harbor a high risk of malignant transformation. It is conceivable that most IPMNs with involvement of the main duct tend to progress to invasive carcinoma over time. Thus, formal oncologic resection is the treatment of choice in surgically fit patients. In contrast, the data regarding BD-IPMN remain equivocal, resulting in conflicting concepts. To date, it is not clear whether and which BD-IPMNs progress to carcinoma and how long this progression takes. **Conclusion:** While patients with MD-IPMNs should undergo surgical resection if comorbidities and life expectancy permit this, the management of small BD-IPMNs remains controversial. Population-based studies with long-term follow-up are needed to define which cohort of patients can be observed safely without immediate resection.

## Introduction

Large cross-sectional studies using modern abdominal imaging modalities such as magnetic resonance imaging (MRI) or computed tomography (CT) have shown that approximately 2% of the general population exhibit cystic lesions in the pancreas [1, 2]. Most of these lesions were found in asymptomatic patients who underwent abdominal imaging for non-pancreas-related abdominal symptoms including urologic, gynecologic, vascular, or other medical conditions [3]. The incidence of cystic pancreatic lesions increases with age and reaches a level of up to 10% in patients of 70 years and older [1]. The majority of authors assume that a large proportion of these lesions represent small intraductal papillary mucinous neoplasms (IPMNs) of the pancreas [2, 4]. However, in the majority of cases there is no histopathological diagnosis available to confirm this assumption. IPMNs are a distinct entity of cystic pancreatic neoplasms characterized by mucin production, cystic dilation of the pancreatic ductal system, and intrapapillary epithelial growth [5, 6]. Moreover, IPMNs are believed to undergo an adenoma-carcinoma sequence eventually culminating in invasive ductal adenocarcinoma over time [3]. Few issues in gastrointestinal medicine are discussed as controversially as the adequate management of patients with these pancreatic lesions [4]. Particularly the role of side-branch IPMNs that exclusively involve the branch duct system of the pancreas is not entirely understood [7–9]. While a number of clinical series have shown that conservative observation of small branch-duct IPMNs (BD-IPMNs) without specific risk factors is safe over extended time periods [10], other studies have reported that in a significant number of surgically resected BD-IPMNs, high-grade dysplasia or even invasive carcinoma was found on surgical pathology [11–14]. To date it is not known whether and which IPMNs harbor the risk of malignant transformation and over what time period malignant transformation develops.

The aim of the present article is to summarize current evidence about the natural history of IPMNs. Moreover, the reader should gain insights into the current controversial discussion about the adequate therapeutic management of patients with these lesions.

## Epidemiology

IPMNs usually occur between the sixth and seventh decade of life and are mostly located in the head of the pancreas [10, 15, 16]. Considering all IPMN patients, an almost equal gender distribution is found; however, more recent studies suggest that BD-IPMNs may occur slightly more often in females [17, 18]. While older studies have reported that approximately 25% of IPMNs are asymptomatic at the time of discovery [19, 20], recent series found that up to 60% of cystic pancreatic neoplasms are discovered accidentally [18, 21]. When patients with IPMN present with symptoms, they frequently suffer from abdominal pain, weight loss, jaundice, steatorrhea, new onset of diabetes, or pancreatitis [15, 20, 22, 23]. Most IPMNs occur spontaneously and without evidence of a systemic or familial disease. However, it has been reported that IPMNs may also arise in the background of inherited syndromes such as Peutz-Jeghers syndrome [24] or familial adenomatous polyposis [25]. A small subset of patients with IPMN is associated with a specific phenotype of familial pancreatic cancer [26]. Beside familial pancreatic cancer, patients with IPMN are in general at a higher risk of developing concomitant pancreatic cancer, either synchronously or metachronously. This is an important observation because it indicates that resection of an IPMN only reduces the risk of developing pancreatic cancer but does not abolish it. The risk has been described to be as high as 10% [27], and there is growing evidence that patients with IPMN, as opposed to patients suffering from spontaneous ductal adenocarcinoma, are also at a higher risk of developing primary extrapancreatic malignancy [28]. For example, patients with IPMNs have a significantly higher risk of harboring colon polyps with consecutive colon cancer compared to the general population. Therefore, colonoscopy should be considered in all IPMN patients for screening purposes [29].

## Pathological and Histopathological Background

Macroscopically, IPMNs appear as mucin-producing, predominantly papillary cystic neoplasms that probably arise from the epithelium of the main pancreatic duct (MD-IPMN), from its side branches (BD-IPMN), or from both (mixed-type IPMN) [30]. It remains controversial whether mixed-type IPMNs arise from either MD- or BD-IPMNs or if they represent a distinct entity [8]. The majority of IPMNs occur in the head or uncinat process of the pancreas [16, 23]. However, in approximately 15% of cases the lesions are multifocal, eventually involving the entire pancreatic gland [7, 23]. In some cases, the lesion presents as multicentric, forming clusters of cysts [31].

Considering the histopathological examination, surgically resected IPMNs frequently display a wide range of dysplasia ranging from low-grade and moderate epithelial dysplasia (formally called ‘adenoma’ and ‘borderline’ lesions, respectively) way through to high-grade dysplasia (‘carcinoma in situ’) and frank invasive adenocarcinoma. Since a time lag of approximately 5 years was observed between patients presenting with benign IPMN and those presenting with malignant IPMN including high-grade dysplasia and adenocarcinoma [6], current thinking is that a progression from preexisting low-grade dysplastic lesions to frank invasive cancer develops over time [32]. It has been reported that this disease progression is associated with cumulative genetic alterations, including a number of mutations known from sporadic ductal adenocarcinoma such as *KRAS* and *TP53* [33].

Beside the location of the IPMN with regard to involvement of the main pancreatic duct or its side branches, it has recently become clear that four histological subtypes of IPMNs can be distinguished [34]: gastric, intestinal, pancreatobiliary, and oncocytic. These subtypes can be distinguished by morphology only as well as by their characteristic mucin expression pattern, particularly with regard to MUC1, MUC2, and MUC5AC. There is growing evidence that these four subtypes are associated with a different risk of malignant transformation and different clinical outcomes. Concerning invasive carcinoma arising in IPMN, three distinct histological subtypes can be distinguished: tubular, colloid, and oncocytic [30]. Analyzing the outcome of these three subtypes of IPMN, it has been observed that the more favorable outcome of patients with invasive IPMN compared to sporadic ductal adenocarcinoma [6, 20, 23, 35] can only be demonstrated for colloid and oncocytic carcinomas [36]. In contrast, tubular adenocarcinoma was associated with an even poorer outcome compared to that of sporadic pancreatic cancer [36].

Today, it is widely accepted that MD-IPMNs exhibit a significantly higher risk of malignant transformation than BD-IPMNs [10]. The risk of harboring malignancy in MD-IPMNs is as high as 45% for invasive carcinoma, with an additional risk of 20% for harboring high-grade dysplasia (carcinoma in situ) [37]. Therefore, international guidelines recommend surgical resection for MD- and mixed-type IPMNs provided that the patient is an adequate candidate for surgery [10, 38] and that comorbidity and life expectancy do not preclude this option. In contrast, it has been proposed to conservatively observe small BD-IPMNs without immediate resection. In recent years, a number of clinical series have been reported demonstrating the natural course of BD-IPMNs. Due to conflicting results of these studies and the difficulty to correctly diagnose malignancy in BD-IPMNs preoperatively, there remain great differences in the management recommendations – particularly for small and asymptomatic BD-IPMNs [39].

## Diagnostic Work-Up for Cystic Pancreatic Lesions

The diagnostic work-up for cystic lesions of the pancreas should definitely include thin-slice cross-sectional studies by CT scan or

MRI [40]. Using these modalities, detailed information about the location, cyst size, and potential relationship to blood vessels or other structures can be obtained. A dilation of the main pancreatic duct of  $\geq 1$  cm strongly suggests MD-IPMN, whereas a mucinous cystic lesion with communication to the main duct but without main duct dilation indicates BD-IPMN [41]. In addition to cross-sectional imaging, a number of diagnostic means have been described to be useful for correctly diagnosing IPMN. Endoscopic ultrasound (EUS) is widely established and recommended in the preoperative work-up of IPMNs [10] and, together with MRI/MRCP (magnetic resonance cholangiopancreatography), better at detecting a communication between a cystic lesion and a pancreatic duct than CT scans. While some authors report that contrast-enhanced EUS might be the most reliable tool to detect mural nodules within the cystic lesion and to accordingly distinguish benign from high-risk/malignant IPMN [12, 42], others stated that mural nodules were found only in a minority of patients even when malignancy was already established [14, 43]. Furthermore, even though EUS in combination with fine needle aspiration (FNA) is often used to establish malignant transformation, a negative finding does not always rule out malignancy [14]. In any case, it is obvious that the use of EUS and FNA is strongly dependent on the experience of the operator [44]. Likewise, the evaluation of cytology following cyst fluid aspiration correlates with the experience of the involved pathologist. While cyst fluid carcinoembryonic antigen (CEA) was shown to be helpful in differentiating between benign pancreatic pseudocysts and potentially malignant mucinous neoplasms [45], this parameter is of limited value in detecting malignancy in a mucinous lesion [46]. Recently, there has been evidence that the serum tumor markers carbohydrate antigen 19-9 (CA 19-9) and CEA are useful tools in distinguishing between benign and invasive IPMN [18, 47]. However, these markers are not suitable to identify obligate precancerous lesions such as IPMNs with high-grade dysplasia that should be considered for surgical resection before malignant transformation occurs [47]. Once they are significantly elevated, the underlying tumor has often progressed to a stage where it is no longer operable.

In summary, all available preoperative diagnostic tools have their limitations, and to date, there is no method available to discriminate between benign and malignant IPMN with a high degree of certainty [13, 48]. This issue needs to be taken into account for choosing the best therapeutic approach in each individual patient although current guidelines suggest that a diameter of  $>3$  cm and the presence of mural nodules should tip the balance in favor of a surgical approach.

### Observational Studies for BD-IPMNs

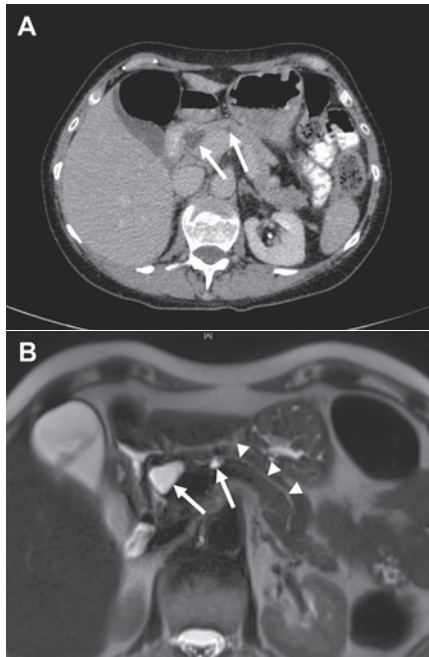
The revised 2012 international consensus guidelines defined so-called 'worrisome features' and 'high-risk stigmata' in order to determine treatment recommendations for BD-IPMNs [10]. According to these treatment recommendations, patients identified with cystic lesions with 'high-risk stigmata' such as obstructive jaundice,

an enhanced solid component within the cyst, or an increasing cyst size over time should undergo resection without further diagnostic evaluation. In contrast, for cysts with 'worrisome features' such as a cyst diameter of 3 cm or more, a thickened or enhancing cyst wall, or non-enhancing mural nodules, further diagnostic evaluation using EUS and FNA cytology is recommended. According to the current international guidelines, for asymptomatic cysts without any of these criteria, observation without immediate resection is recommended [10].

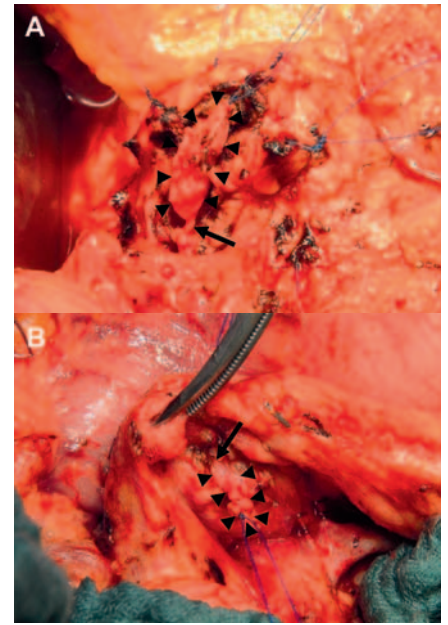
There are several large retrospective series available that validated the safety of these recommendations, encompassing more than 250 patients [23, 31, 49]. In none of the patients in these series who met the criteria for conservative observation but still underwent pancreatic resection, cancer was found in the surgical specimen. Moreover, two recent studies confirmed the management guidelines, stating that following the observation recommendations is safe, whereas caution is advised for larger cystic lesions [18]: Jang et al. [50] reported that the new consensus guidelines provided better sensitivity, performance of factors predicting malignancy, and balanced accuracy in the diagnosis of BD-IPMN malignancy. However, in contrast to other studies, Jang et al. [50] found that size alone was of limited accuracy for predicting malignancy. Kobayashi et al. [51] reported that even when small mural nodules of  $<1$  cm in diameter were found, observation was considered safe due to a low risk of malignant transformation. It should be noted here that while the mural nodules are an indicator for the risk of malignant transformation, the cancer does not necessarily arise from these nodules but in other portions of the cystic lesion [51]. Two recent series examined the risk of malignancy in BD-IPMNs with minimal or limited involvement of the main pancreatic duct [52, 53]. The authors of both studies conclude that primary surveillance of mixed-type IPMNs might be reasonable in selected patients. However, in the study of Roch et al. [53], among 70 patients with mixed-type IPMN, 9 (13%) showed a progression to invasive carcinoma at a mean of 3.5 years (range: 1–9 years).

With regard to long-term follow-up studies, it remains unknown when the neoplastic transformation from benign IPMNs to malignant lesions begins [9, 41]. It was suggested that disease progression occurs in 10–40% of the patients over 5 years, and the calculated risk of cancer development is approximately 20% over 10 years [9, 41]. It is well established that patients with IPMN are not only at a higher risk of developing IPMN-associated adenocarcinoma but also of concomitant sporadic pancreatic cancer, either synchronously or metachronously [27]. In these cases, the IPMN indicates only the tip of the iceberg of a pancreatic field defect [54], leading to neoplastic changes over time [7]. It also denotes that resecting the IPMN does not necessarily abolish the risk of pancreatic cancer and that patients have to remain in postoperative surveillance programs. In spite of such a follow-up, the progression to invasive cancer can be missed, as has been reported in patients who developed non-resectable pancreatic cancer during close follow-up after IPMN resection [9]. Not only this issue but also the potential of non-compliance during follow-up always has to be balanced against the risk of surgical resection in each individual patient [55].

**Fig. 1.** Two small BD-IPMNs in the head and corpus of the pancreas. **A** CT imaging showing two hypodense cystic lesions in the pancreatic head and corpus (arrows) of a 52-year-old female. In maximal diameter, the lesions measured 2.2 and 1.4 cm, respectively. **B** T2-weighted MRI exhibiting both lesions (arrows) and an unremarkable and thin pancreatic main duct (arrow heads).



**Fig. 2.** Surgical pancreatic enucleation of two small BD-IPMNs. Enucleation of two small BD-IPMNs (arrow heads) in the pancreatic head and corpus of a 52-year-old female (see fig. 1). **A** Enucleation of the BD-IPMN measuring 2.2 cm in the pancreatic head. **B** Enucleation of the lesion measuring 1.4 cm in the corpus of the pancreas. For the surgical approach of this lesion, the dorsal part of the pancreatic gland was mobilized by dissection of the splenic vein. Both cystic lesions revealed a visible branch duct with direct connection to the main pancreatic duct (arrows). The final histological examination revealed two BD-IPMNs with low-grade epithelial dysplasia.



### Surgical Series of Resected BD-IPMNs

According to the current guidelines, younger patients (<65 years) with a cyst size of >2 cm may also be candidates for resection [10], owing the cumulative risk of malignancy over time [12, 56] and their life expectancy. In recent years, an increasing number of surgical series has been published reporting that also small and unsuspecting BD-IPMNs may harbor a significant risk of malignancy in up to 20% of the cases [11–13, 57]. Wong et al. [14] found that high-grade dysplasia and adenocarcinoma were found in BD-IPMNs measuring less than 3 cm on EUS. Salvia et al. [48] reported that even in an experienced pancreatic center inaccurate preoperative diagnosis for cystic pancreatic lesions approached 22%. Likewise, Barron et al. [58] found that the preoperative radiographic IPMN type did not correlate with the final pathology in 25% of the patients. The authors suggest considering serum CA 19-9 as a complementary tool within the context of preoperative evaluation of cystic lesions [48]. Indeed, in a recent systematic review by Goh et al. [59], the limitations of the Sendai consensus guidelines were confirmed. The positive predictive value of the guidelines for predicting a malignant BD-IPMN was low, and some malignant lesions might be missed when diagnosis is based on these guidelines [59]. In this study, among 690 surgically resected BD-IPMNs, a malignancy rate of 24% was found. The strength of this study is that for each patient the final histological diagnosis was available. However, the incidence of malignancy only refers to patients who underwent surgery. It is possible that the real incidence of malignancy in BD-IPMNs is much lower because experienced clinicians were more likely to select patients at an increased risk of malignancy for resection. Surgeons often decide on resection based on a number of clinical factors that were not implemented in the international consensus guidelines, such as serum tumor markers, age, and previous extrapancreatic malignancy (e.g. breast cancer), and other unknown criteria [43, 60]. This assumption is also

supported by the study of Roch et al. [53] who reported that the criteria mentioned in the international consensus guidelines carried an unequal weight and were not cumulative in the prediction of risk for malignancy or invasiveness in IPMN.

In many cases, instead of a formal oncologic resection, a pancreatic parenchyma-sparing operation such as an enucleation can be considered for BD-IPMNs, even when they present multifocally (fig. 1). Depending on fresh-frozen section histology, the surgeon can decide whether a formal resection is necessary for the adequate treatment (fig. 2). Pancreatic enucleations can be performed with low morbidity and no mortality in high volume centers [61] and therefore represent an alternative to formal oncologic resections. In view of the fact that a significant risk of developing pancreatic cancer remains even after successful oncological IPMN resection, a more limited approach to either confirm or refute the malignant nature of a cystic lesion appears reasonable.

### Summary of Current Evidence

To date, there remain conflicting results particularly concerning predictors of malignancy in both MD- and BD-IPMNs. Therefore, the natural history of this disease is not entirely understood. It is conceivable that in analogy to the natural history of colon polyps, an adenoma-carcinoma sequence exists in IPMNs. We believe that lesions with high-grade dysplasia have to be considered as high-risk lesions that transform into invasive cancer over time as well as at a significant rate. With regard to current scientific knowledge and the absence of truly population-based (rather than case series-based) studies, it is impossible to determine the real incidence of malignancy in small cystic lesions that have not been resected. It is

probable that a number of small BD-IPMNs that are under surveillance already harbor small areas of invasive cancer that would only be detected by histological examination after surgical resection. This would be in analogy to prostate cancer which can be present for many years before becoming clinically apparent [39]. In contrast, it is also conceivable that some BD-IPMNs do never progress or undergo malignant transformation. To date, it remains difficult and sometimes impossible to predict malignancy correctly in IPMNs. Without any doubt, the international consensus guidelines are helpful to identify patients with a high-risk profile. However, the indication for surgical resection always has to be seen individually in each patient. Factors such as age, life expectancy, comorbidity, family history, or the willingness of the patient to undergo surveillance have to be considered for an adequate therapeutic management. The decision making for a colon polyp with its adenoma-carcinoma sequence is easy. A snare polypectomy carries a mortality risk of less than 1:10,000, and morbidity is also very low. For prostate and breast cancer the decision is more difficult, and the pendulum has swung from concerns about catching all high-risk or malignant lesions early (and resecting them) to a much greater concern about overtreatment because the associated morbidity is significant and may outweigh the benefit of early detection and resection. For potentially malignant lesions of the pancreas the risk assessment is infinitely more complex: Not only is an overlooked pancreatic cancer invariably a death sentence but the risk of overtreatment also carries the risk of a postsurgical mortality of 3–8% and a morbidity of 30%.

It is well known that the prognosis of patients with resected IPMN with low-grade, moderate, or high-grade dysplasia is excel-

lent with a 10-year disease-specific survival of >95% for both MD- and BD-IPMN [37]. Recurrent disease is mainly found in patients with BD-IPMNs or in those with MD-IPMN and a false-negative transection margin because of denuded epithelium. For patients with invasive IPMN, the 5-year overall survival is around 40% [62]. To date, it remains controversial whether this better survival compared to sporadic ductal adenocarcinoma is related to an earlier stage of presentation or due to a different biological behavior of mucinous cystic neoplasms – or both [3].

## Conclusion

MD- and mixed-type IPMNs principally have to be considered as precursors to invasive adenocarcinoma of the pancreas. The tumors likely undergo an adenoma-carcinoma sequence eventually culminating in malignant neoplastic transformation. In contrast, the role of BD-IPMNs is not entirely understood. It is not clear whether all BD-IPMNs harbor a risk and malignant potential of malignant transformation and what the timeline of growth and progression might be. Therefore, the indication for surgical resection versus observation has to be individualized depending on a number of clinical factors. Clinical decision making should always be based on the expert opinion of an interdisciplinary team of gastroenterologists, radiologists, and surgeons in a pancreatic high-volume center.

## Disclosure Statement

The authors declare no conflict of interests.

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