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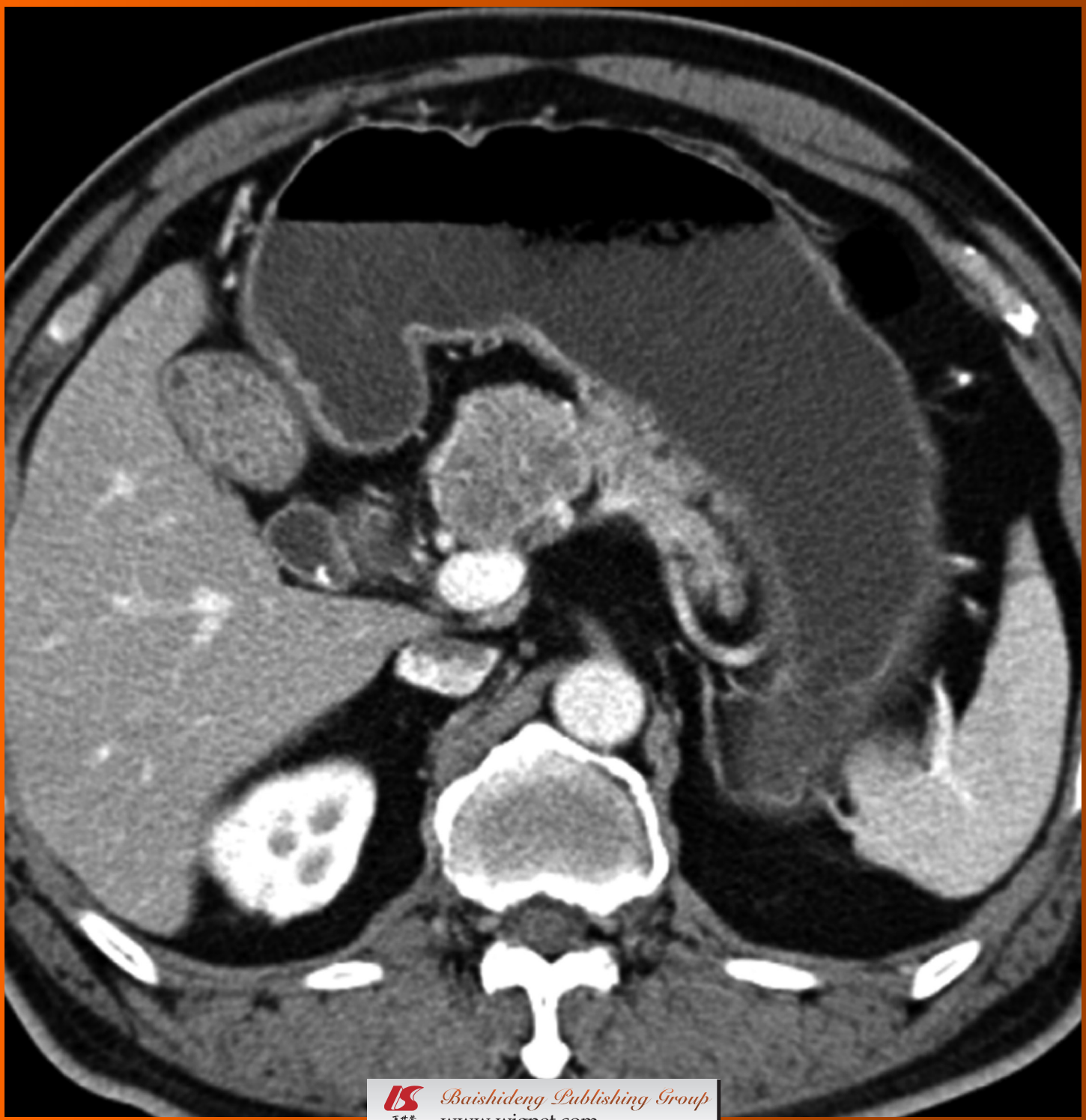

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EDITORIAL

Intraductal papillary mucinous neoplasm: Coming of age

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Abstract

Intraductal papillary mucinous neoplasm (IPMN) is a disease in evolution. Since its first description almost 30 years ago, a better understanding of the disease has steadily accrued. Yet, there are numerous challenges still for clinicians who treat this fascinating disease. A group of leading content experts on IPMN was assembled and charged with presenting cutting-edge knowledge on various topics for which they have considerable experience. This manuscript provides an historical perspective of both clinical and biological quandaries that have been resolved to date. Furthermore, it poses new avenues for investigation while highlighting the contributions of the various authors to this collective review.

Key words: Intraductal papillary mucinous neoplasm; Natural history; Pancreatic surgery

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INTRODUCTION

It has been nearly three decades since the original description by Ohashi of what we now refer to as intraductal papillary mucinous neoplasia (IPMN). What a ride of discovery it has been to our present understanding of this disease. Yet, do we really understand it? The evolution of IPMN might be viewed through an analogy to human development. At this point in time, it is neither child nor adult. Instead, like an adolescent who simultaneously displays elements of maturity, intrigue and potential, IPMN is just now coming of age.

To date, enough evidence has accrued for us to accurately recognize this condition and, more importantly, treat it with relative success. Along the way, key building blocks to this foundation include the recognition of IPMN being a malignant precursor lesion, the segregation of biological impacts of various IPMN morphologies, the development and general adoption of consensus management guidelines and numerous significant clinical series which confirm successful perioperative and oncological outcomes following definitive surgical intervention. Landmark events in the lifespan of IPMN which have contributed to these underpinnings include the original Ohashi description (1982), the WHO consolidation of nomenclature (1996), the Sendai Conference (2005) and now the era of the incidentaloma (2000s - onward).

Yet, ultimate mastery of this disease eludes us and there is undeniably so much more to comprehend. For instance: Is malignant IPMN the same disease as sporadic pancreatic adenocarcinoma? Is the whole pancreas vulnerable in a "field-defect" manner? When do IPMNs first manifest and how fast do they progress? Will clinicians ever be able to accurately identify the degree of dysplasia before the pathologist? When is the ideal time to definitively intervene? Is observation a safe, economical and/or efficient means of therapy? Burning questions all.

To gain traction on these and other issues, we have compiled a series of invited reviews from recognized thought-leaders in the field. Discrete topics were assigned according to the author's demonstrated expertise and contributions to the field. While each of these manuscripts

can be stand-alone offerings, we present them collectively to weave a tapestry which reflects the complexity of IPMN. As you read these papers, you will realize that IPMN is the epitome of a multidisciplinary disease. Each author succinctly, but thoroughly, reviews a topic, while also editorializing based on their considerable personal experience with the disease. Naturally we could not cover all topics pertinent to IPMN. Instead, we purposefully chose themes which, so far, are well established yet still stimulate controversy.

What follows is a short synopsis of what you'll enjoy in each of these contributions. Each paper is distilled down to its crucial take-home points and food-for-thought is offered.

BIOLOGY OF INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM

While this collection of papers largely features the significant clinical acumen we have thus far accrued about IPMN, we crave more clarity on its basic biological processes. Caroline Verbeke, a renowned pancreatic pathologist from Leeds, UK, beautifully and succinctly informs us that we actually know more that we might think[1]. Through an organized review of gross, histological and molecular pathology, she muses how a "panoply" of different morphological and cellular features might arise from a unified precursor (normal ductal epithelium). Histologically, IPMN is often compared to the classic colonic "adenoma-to-carcinoma sequence", yet is there real evidence to support this generalization?

What may not be well appreciated by clinicians at the macroscopic level is the fact that the majority of IPMN, like adenocarcinoma, is situated in the head of the gland. While we now have a good grasp on the relevance of Branch-duct and Main-duct disease, do we understand the implications of such histological subtypes as intestinal, pancreaticobiliary, colloid or oncocytic IPMN? She suggests that location of disease in the ductal system is not randomly assigned but rather due to intrinsic biological programming. Some feel that the pancreas is vulnerable to IPMN development in a "field defect" setting. Apropos to this, the concept of "unstable ductal epithelium" is addressed as well as the fact that IPMNs are not crisply delineated but rather surrounded by a "grey zone" of cells with various molecular activity. Indeed, at the molecular level, common genetic manifestations of neoplasia such as gene mutations, chromosomal imbalances, aberrant methylation and microsatellite instability are regularly observed in IPMN.

Finally, new avenues of investigation are proposed, including the sorely needed development of functional animal models to study this disease. There is huge potential to study IPMN as a coordinated biological system - linking genetics to biochemistry to cellular and then tissue elements. Hopefully with better clarity of these fundamental issues will come improvements in diagnostics, prevention and therapeutics for the patient.

IS THIS REALLY AN EPIDEMIC? THE EPIDEMIOLOGY OF INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM

To those on the frontlines of IPMN care, it seems as if we are in the midst of an epidemic. But is it? As most of the data accrued on the topic has been derived from pancreatic specialty centers, our impressions regarding the incidence of this disease are undoubtedly biased and probably over-estimate its true scope. Reid-Lombardo and colleagues from the Mayo Clinic have taken a step back and attacked this question from a population-level perspective[2]. They lead off by presenting work from their institution which suggests that IPMN actually occurred prior to the landmark Ohashi description in 1982. This retrospective pathological analysis of pancreatic cysts dating back to the 1960s is important in that it shows that IPMN is not necessarily a new disease but rather a newly recognized disease. Since then, there has naturally been an evolution in the nomenclature and classification which has aided in standardized acceptance.

The authors then share the findings of their population-based analysis using a unique medical records linkage system in their region dating back to 1984. For this particular populace, the incidence is low (on the order of 2 per 100 000 person-years) but has been on the rise over time. The authors are quick to point out, however, that this does not rise to the level of an 'epidemic'. The point prevalence is 26/100 000 cases but much higher for those patients over 60 years of age. The average diagnosis was made at age 73 years and most patients were asymptomatic. The authors also point out that while detection of malignant IPMN is decreasing, rates of resection for IPMN appear to be on the rise - both trends are probably due to earlier detection.

Next, they touch on putative risk factors for IPMN and propose that pancreatitis is likely to be the effect of IPMN rather than the cause. They argue that due to the absence of any identified environmental risk factors to date, genetic analysis is likely to be more promising in understanding the genesis of this disease. Lastly, they touch on the concept of screening patients both for and with IPMN. This notion weaves together many concepts from elsewhere throughout this collection. Might it be that we are already, in effect, unwittingly "screening" for IPMN by the progressive reliance of diagnostic imaging studies occurring ubiquitously in medicine? Which brings us to…..

BRAVE NEW WORLD OF THE INCIDENTALOMA

At the outset, most cases of IPMN presented in a symptomatic fashion - usually as abdominal pain and often with biochemical evidence of pancreatitis. Most would remark that, in this early era, the majority of the disease was bulky, grossly-evident, Main-duct disease. But, my, how times have changed! Now, driven by the advances in diagnostic imaging and other technologies, we are more apt to

encounter small, Branch-duct cysts and with increasing frequency. In fact, the work-up of cystic lesions has now risen to equal footing with the more traditional reasons for referral to a pancreatic surgeon - pancreatic cancer and pancreatitis. With the advent of this new category, uncertainties abound - quandaries over accurate diagnosis, management approaches and timing of interventions.

Kent *et al*[3] from the pancreatic surgical unit at Beth Israel Deaconess Medical Center at Harvard University first depict the global scope of the problem and then review their own considerable experience with asymptomatic pancreatic lesions (APLs). They provide a sensible management approach which relies on a multidisciplinary system incorporating specialists in advanced endoscopy, radiology and pancreatology. While they note that APLs constitute a wide spectrum of pathology (solid/cystic, benign/premalignant/malignant), they clarify that for all APLs, IPMN is now the most common diagnosis. This holds up specifically for cystic APLs as well (up to one-third). What is more troubling is the fact that 11% of cystic APLs in their series were malignant. So the primary question is, "Do all incidentally identified IPMN require surgical resection for a relatively low (yet real) risk of cancer?" The answer - probably not.

The authors then review the influence of the Sendai Consensus Guidelines for mucinous neoplasms which, although arguably imperfect, have served as a standard for management of IPMN since 2006. These guidelines reason that most Branch-Duct IPMN can be observed serially - particularly the type we are now regularly encountering incidentally - the small, 1-2 cm lesion devoid of any suspicious features. It seems that over the last decade, for most pancreatic surgeons, the pendulum has swung from a resect-first mentality to a cautious strategy of observation. So, if observation is the new paradigm, when, if ever, would we operate and what is the cost of our action or inaction? The authors suggest that one significant but under-appreciated byproduct of this observation strategy is a heightened sense of anxiety which is a burden for both the patient as well as the surgeon. There are considerable consequences to acting either too early (complications, pancreatic insufficiency) or too late (advanced malignancy). In the end, the decision usually comes down to philosophy; are you (and your patient) aggressive or cautious?

BRINGING IMAGING INTO FOCUS

Given that clinical management decisions pivot on accurate identification of IPMN from its mimes as well as the ability to distinguish variations of the disease, accurate imaging of the pancreas is a cornerstone in the care of the patient with IPMN. In fact, radiographical analysis remains the most practical and valid, if certainly imperfect, means of making the diagnosis today. The predictive correlation between radiology and pathology has never been better. Yet, to attain this, we must use state-of-the-art tools with proper protocols to achieve the best accuracy. But, while we may be confident in ascribing a basic pathological diagnosis to any given lesion of the pancreas through radiographical means, we still lack the ability to predict the degree of disease (i.e. dysplasia *vs* invasive malignancy), short of histological biopsy. Perhaps just as important to the techniques employed may be the reader of the scan, and today we have a proliferation of pancreatic imaging experts populating most high-volume pancreatic units worldwide.

Pedrosa and Boparai from the renowned pancreatic imaging group at Beth Israel Deaconess Medical Center in Boston, update us on modern concepts and controversies in IPMN imaging[4]. They first illustrate the seminal role that ever-more-prevalent imaging has had in spawning the "incidentaloma" phenomenon. The authors inform us that while communication between side-branches and the main duct can be ascertained (particularly well by MRCP), we still struggle with differentiating tumor nodules from mucin globules. They suggest that cyst size alone is not the be-all, end-all; without evidence of other complex features, cysts are unlikely to be malignant. Finally, they address the nuances of surveillance protocols for IPMN, both in the preoperative state (presumed IPMN) and the post-resection follow-up of the pancreatic remnant in cases of known IPMN. While it may satisfy us as clinicians to aggressively monitor our patients with top-end imaging, should we be concerned about the implications of this policy? Specifically, can the anxious patient tolerate the uncertainty of observation? Are there effects of cumulative radiation exposure? Is surveillance actually cost-effective? These questions are ripe for properly designed clinical investigation.

WHAT'S IN THE DIFFERENTIAL?

One of the basic tasks of the pancreatic surgeon is to make an accurate diagnosis of IPMN before undertaking a treatment plan. Put simply, we need to know exactly what process we are dealing with. Unfortunately, the pancreas harbors a variety of cystic lesions with a full spectrum of pathology but only a fraction of these will be IPMN. But, to best recognize IPMN, you must first understand it. Based on their institution's extensive experience with pancreatic diseases, Cunningham, Hruban and Schulick from the Johns Hopkins Medical School were invited to highlight their trailblazing experience with IPMN (136 resections)[5]. They then develop how cystic lesions can be characterized by "patterns" of clinical, radiographical and biochemical data and continue by sharing with us a remarkably intuitive algorithm for differentiating IPMN from other confounding pathologies. In essence, they suggest conducting the investigation by a process of elimination rather than the more traditional approach of developing a differential diagnosis. This cogent and simple reasoning approach, condensed beautifully in a table, concentrates on demographics, imaging, cyst fluid analysis and, finally, histology. Unfortunately, they acknowledge that all too often, the final diagnosis is in question until the pathologist's definitive review. But with accrued ex-

perience, we clinicians should do better at prediction of IPMN as our familiarity increases. They bring to question the ubiquitous employment of the Sendai consensus guidelines, hinting that there may be more distinct indications for resection which seem to differ based on various institution's own experience with the disease. Last, they introduce the emerging use of Markov modeling and nomograms for decision making in IPMN. These tools attempt to simplify the complexities of individualized patient care… but is it really that easy?

IS LESS BETTER? PART 1 (MINIMALLY INVASIVE TECHNOLOGIES)

As a natural extension of this topic, endoscopic techniques have long played a critical part in the diagnosis and management of IPMN. Of course, we are all familiar with the seminal description of IPMN presenting *via* upper endoscopy as a gaping, mucous-extruding "Fish-Mouth" papilla. However, this "classic" presentation is in fact all too rare these days as most disease is now initially recognized by axial imaging in the new era of incidentalomas. Nonetheless, the application of endoscopy for IPMN continues to increase. Seminal in this growth has been the employment of cyst fluid analysis and the gastrointestinal endoscopy group at the Massachusetts General Hospital has been in the vanguard of this process. In this paper, Turner and Brugge describe the merits of ERCP, EUS and fine-needle aspiration and they emphasize the additive value of biochemical and molecular analysis over cytology alone[6]. Newer diagnostics, like Narrow Band Imaging and Optical Coherence Tomography so far applied to the biliary system, are introduced to us as emerging options for interrogating the pancreatic duct for evidence of neoplastic change. While peroral pancreatoscopy is also alluded to, we are left to wonder why practitioners in the West have not found as much utility in this modality as have those from the Orient? Finally, the authors offer ground-breaking and somewhat controversial prospects that endoscopic-guided ablative technologies may soon be in the arsenal against IPMN. Initially, at least, these provide new horizons for patients who can not, or should not, be resected. Yet, it is not hard to envision there may come a point when such minimally invasive therapeutics will become first-line options.

MAKING THE DISTINCTION

Perhaps the single most important clinical breakthrough in the IPMN story was the realization that Branch-Duct cysts are different from Main-Duct disease. The distinguished investigators from Verona led by Claudio Bassi have been pioneers in IPMN investigation and have emphasized the clinical importance of this distinction[7]. Central to this is the awareness that invasive malignancy is far more common (50%-75%) in Main-Duct disease. The original description by Ohashi in 1982 represented what was most apparent at that point in time - symptomatic, grossly evident Main-Duct disease - and the initial stance by clinicians was to act proactively on all such presentations. Yet the playing field has been altered dramatically in the ensuing decades by imaging advances which are gradually identifying more and more subtle findings in asymptomatic patients. Although not yet proven, with this trend undoubtedly comes a higher proportion of Branch-Duct discovery. An important by-product of this dogma has therefore been the gradual adoption of a more cautious tone regarding these Branch-Duct cysts.

The authors note that while there are in fact similar demographic factors between the two categories, Main-Duct disease differs by being more clinically evident; the overwhelming majority of cases are symptomatic (manifest by jaundice, weight loss, diabetes *etc*.). In a landmark study in conjunction with the Massachusetts General Hospital (140 patients), the authors found that the development of malignancy in Main-Duct disease lagged by over six years from patients harboring premalignant dysplastic lesions. Interestingly, no such relationship exists for Branch-Duct cysts. Why is this? The authors suggest that the discrepancy in malignant behavior may be explained by the segregation of the inherently more threatening intestinal-type histology with Main-Duct morphology. Also, yet to be understood is the clinical relevance of the so-called "Mixed-Duct" or "Combined" version of this disease. Is this a unique entity or simply a local extension of one of the other morphologies? To date, the evidence suggests they behave similarly to the more aggressive Maid-Duct variant. If so, an important question then becomes…. "Can these combined types be accurately distinguished preoperatively?"

IS LESS BETTER? PART 2 (EXTENT OF RESECTION)

Basic surgical decision making obeys three rules: "When to operate?", "What type of operation?", and "How much operation?" One of the unique dilemmas in oncological surgery is striking the appropriate balance between adequately removing the malignancy *vs* maintaining sufficient organ function. Fortunately, as the safety of pancreatic surgery has improved and the technology has evolved, we now have more arrows (procedures) in the quiver than ever before. Thus, when deciding on what operation to perform, pancreatic surgeons are constantly walking the tight-rope of how much - weighing oncological efficiency against complications. Explaining this reasoning to the patient is also a critical element of the informed consent process. In the case of total pancreatectomy, diabetes and exocrine insufficiency are absolute but for most pancreatic hemi-resections the chances fall to the 25% range. Can we do even better while optimizing survival?

Falconi and his colleagues from the Verona surgical unit have a rich experience with this topic[8]. Their first principle is to tailor the operation to the morphology and topography of the disease. For Main-Duct disease, the difficulty remains in determining where the actual epicenter of disease is, based upon clinical and radiographical

parameters. Does this presentation require total pancreatectomy *de facto*? Probably not. Yet, given the high malignancy rate, an adequate lymph node harvest is considered requisite in whatever procedure is applied. They note from their experience with malignant IPMNs that 42% had positive LN involvement which is significantly less than traditional pancreatic adenocarcinoma (in the order of 80%). Survival is certainly affected negatively in this case and the ratio of positive to total lymph nodes is also predictive. Still, total pancreatectomy should not be feared if it is the best option for complete oncological control, especially given the dramatically improved perioperative outcomes and postoperative glucose control currently being achieved. The authors caution about the use of parenchymal-sparing (central pancreatectomy) and laparoscopic procedures for this variant. They tackle the issue of intraoperative transaction margin analysis, feeling that it is generally effective and accurate and can facilitate decision making. They do stress that specimens with denuded epithelium are problematic and should be considered positive for invasive malignancy until proven otherwise.

In terms of decision making for Branch-Duct disease: since, in the recent era of more cautious observation, we now only operate on the more onerous lesions, shouldn't these patients by definition receive bigger operations for maximal oncological control? The authors express agreement with this philosophical concept.

IS FROZEN SECTION ANALYSIS HELPFUL?

As surgeons struggle with just how much pancreas to resect for IPMN, the decision to analyze intraoperative transaction margins comes to mind. Sauvanet *et al*[9] from Clichy, France are recognized experts on this controversial topic which has certainly evolved over the last 25 years but is little analyzed in the literature. It was a common practice early in the surgical management of IPMN to progressively cut back on the retained pancreatic remnant until there was no evidence of any dysplasia at the transaction margin. This frequently led to total pancreatectomies or, even worse, compromised or ineffective remnants. My how times have changed in this regard! The authors concentrate on the mechanics of frozen-section acquisition (by both the surgeon and pathologist) which may influence results of the analysis and therefore decision making - perhaps in up to a third of all cases[9]. The use of acquiring sequential frozen sections to avoid more extensive pancreatectomy is emphasized and they stress the different thought processes needed for SB and MD variants.

Like Crippa *et al*[8] above, they explain that de-epithelialized ducts are a common and troublesome dilemma. Of particular interest, they espouse perhaps a more aggressive approach than others, advocating for further resection with the identification of at least adenomatous disease at the margin for Main-Duct disease and the detection of borderline IPMN for branch-duct cases. However, fairly, they concede that management decisions should not be made in the vacuum of the frozen-section histology alone but should take in to account the patient's global picture (age, condition, prognosis, *etc*.). Finally, a novel theme developed in this monograph is the concept of "active *vs* passive" ductal dilation. Is a grossly dilated duct necessarily diseased with neoplastic tissue? How would we know?

MALIGNANCY IN THE BACKGROUND OF INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM: IS IT THE SAME?

Ohashi's initial description of IPMN was actually of four malignancies of the pancreas with morphology (cystic features) unusual for traditionally recognized pancreatic ductal adenocarcinoma (PDAC). Since that point, the specter of cancer has dominated clinical decision making in this disease. Much controversy has ensued regarding the true nature of adenocarcinoma in the setting of IPMN. Is its genetic origin the same as sporadic PDAC? Does it behave similarly? Is the ultimate prognosis equivalently dismal?

To shed light on these quandaries, Yopp and Allen from the Memorial Sloan Kettering Cancer Center in New York have reviewed the accrued data on this topic and provided a thoughtful analysis[10]. While the literature supports an overall five year survival of between 40% to 60% for malignancy in the setting of IPMN (double to triple that of PDAC), there are nuances to consider. For instance, the various histological subtypes (colloid *vs* tubular) differ in their inherent biology. On the tissue level, they respectively align with the intestinal and pancreaticobiliary histologies introduced above by Verbeke. Naturally, they display different molecular profiles as well. From their own institution's considerable experience, the authors point out that both tubular histology and lymph node involvement are negative predictors for survival in invasive IPMN.

What about adjuvant therapy for this disease? They suggest that, given the paucity of evidence, this decision be tailored to the actual biology of any given tumor in appropriately suitable candidates. For instance, smaller tubular tumors devoid of onerous features may not actually benefit, whereas some unfavorable colloid tumors may. The authors explain that the generally encouraging overall survival for invasive IPMN *vis a vis* PDAC may be misleading in that it may be skewed towards a dominance of colloid subtype tumors. The survival for tubular tumors is probably equivalent to that for garden-variety PDAC. Finally, they offer intriguing new evidence from a matched survival analysis employing a novel, post-resection outcomes nomogram developed at their institution. This investigation confirmed the notions that colloid tumors have a favorable prognosis (up to 87% 5 year survival) whereas tubular tumors behave similarly to that of conventional PDAC. The most convincing point, however, is that regional lymph node status appears to be the most

important determinant of prognosis, perhaps trumping the influence of the tumor histology itself.

INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM AND EXTRAPANCREATIC MALIGNANCIES: CLOSE SIBLINGS OR DISTANT COUSINS?

Interestingly, there may actually be a greater understanding about malignancies associated with IPMN than there is about the actual pancreatic malignancy in IPMN itself (above). The simple facts are that up to half of the patients diagnosed with IPMN will manifest some other form of neoplasia (malignant or benign) in their lifetime. Temporally, these can occur before, concurrent or after the diagnosis of IPMN and, as would be expected, the association increases with age. Up to 15% die of these secondary malignancies and not the IPMN itself but thus impact on data for overall survival from IPMN. The question begs… "Is IPMN part of a generalized cancer syndrome?" Furthermore, can we learn more about the derivation of pancreatic cancer through studying the genetic/molecular mechanisms of IPMN development? Benarroch-Gampel and Riall have cogently addressed these issues based on their considerable experience with this topic[11]. They explain the nuances of using both population-based and institutional datasets and conclude that there is a higher incidence of extrapancreatic malignancies in patients with IPMN than in the unaffected general population. Also evident is that secondary malignancies appear to be more frequent in IPMN patients when compared to those patients with straight-forward PDAC. The authors emphasize that conclusions from institutional-based studies should be tempered by realizing that the data is derived from cases of IPMN which have been resected and certainly do not reflect the overall population harboring IPMN.

While a litany of tumors have been described, the most common sites are elsewhere in the gastrointestinal tract but exactly which organ varies around the world. For instance, Oriental's are more prone to upper gastrointestinal lesions whereas Westerners suffer more readily from colonic pathology. This has led to the recommendation that screening endoscopy be incorporated into the regular health-maintenance process for IPMN patients. However, are these diseases really related or is this observation just a by-product of heightened surveillance from the new IPMN diagnosis? Contributing environmental and genetic factors elude us except for the increased prevalence of *MUC2* gene expression in those IPMNs associated with extrapancreatic neoplasms. From the data, most of these lesions are preexisting or concurrently diagnosed; however, our recognition of postoperative occurrences may be masked since the global follow-up of IPMN is relatively short and some will even die from their IPMN before other cancers can manifest. They close by illustrating the clinical implications of this phenomenon and give concrete, albeit unevaluated, suggestions for surveillance in both preoperative and postoperative IPMN scenarios. Still, one wonders if, on the flip side, we should actively screen all patients with recognized GI neoplasias for IPMN?

NATURAL (OR UNNATURAL) HISTORY?

As you will come to recognize, a recurring and binding thread throughout this series of monographs is the frustration with our lack of mastery over the "natural history" of this disease. In managing IPMN, many of our clinical decisions are predicated on ability to predict a certain outcome for any given patient. Unfortunately, given that IPMN has only been recognized as a distinct entity for fewer than 30 years, we woefully lack an understanding of its actual biological behavior. Instead, we are left to rely on our accrued experience to date - evidence which spans less than half a human's lifespan. Ball and Howard attack this topic head-on in a rich and erudite offering that challenges many current assumptions[12]. For instance, many of us consider the dysplastic changes of IPMN to be analogous to the "adenoma-to-carcinoma sequence" - a concept here-to-date best established in relation to colon cancer. The authors suggest the evidence for this to be the case in IPMN is "circumstantial at best" and also question whether the association of Main-Duct disease and invasive adenocarcinoma is indeed causal or not.

Most importantly, they point out that the act of enacting therapy (surgical resection) has precluded our ability to generate a full and accurate understanding of its true natural history. From a practical standpoint, some of this dilemma is explained by the fact that, in any given patient, symptoms force action regardless of the actual malignancy threat. Properly designed observational studies are lacking and needed. Furthermore, they lament that the few observational series we can pull from are hampered by the lack of proven histology as well as extremely short-term follow-up spans. The take-home point of this missive is that the data on which we predicate our current clinical decision making is anemic and the evidence offered is scant.

CONCLUSION

IPMN is a fascinating disease and its identification has, in so many ways, revolutionized the fields of pancreatology and pancreatic surgery. We hope you enjoy this timely compilation of state-of-the-art reviews from noted experts in the field. Certainly you will realize that, while we have come a long way since 1982, we are nowhere near the command of this condition that we, and our patients, yearn for. We hope that this collection of authoritative manuscripts will augment your current understandings of IPMN, inspire study of the current dilemmas and, most importantly, stimulate new avenues of thought and investigation.

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TOPIC HIGHLIGHT

Elijah Dixon, MD, BSc, MSc (Epi), FRCSC, FACS, Assistant Professor, *Series Editor*

Intraductal papillary-mucinous neoplasia of the pancreas: Histopathology and molecular biology

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Abstract

Intraductal papillary-mucinous neoplasm (IPMN) of the pancreas is a clinically and morphologically distinctive precursor lesion of pancreatic cancer, characterized by gradual progression through a sequence of neoplastic changes. Based on the nature of the constituting neoplastic epithelium, degree of dysplasia and location within the pancreatic duct system, IPMNs are divided in several types which differ in their biological properties and clinical outcome. Molecular analysis and recent animal studies suggest that IPMNs develop in the context of a field-defect and reveal their possible relationship with other neoplastic precursor lesions of pancreatic cancer.

Key words: Intraductal papillary mucinous neoplasm; Pancreas; Molecular pathology

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INTRODUCTION

Since the first report on intraductal papillary-mucinous neoplasm (IPMN) of the pancreas in 1982[1] and the recognition of this entity by the World Health Organisation in 1996, it has become increasingly clear that in fact IPMNs constitute a heterogeneous group with a wide range of gross and microscopic features. In this review, the panoply of morphological and molecular characteristics of IPMNs will be briefly discussed along with recent developments that provide new insight into the development of IPMNs and their relationship with other neoplastic precursor lesions in the pancreas.

GROSS

IPMN is defined as an intraductal proliferation of mucin-producing neoplastic cells arranged in papillary formations[2]. Duct dilatation is the key macroscopic feature of IPMN; however, this can vary significantly, depending on the degree of mucin production and papillary tumor formation. The latter can range from a mere granularity of the duct lining to bulky, several centimetres large protrusions within the dilated duct lumen. Similarly, intraductal mucin can be hardly detectable in some cases, whereas in others, copious amounts of mucus cause marked duct distension and occasionally extrude through the papilla of Vater. Gross appearance further depends on which part of the pancreatic duct system is involved and on the extent of the lesion (Figure 1). Any solid or gelatinous nodular areas suggest the presence of associated invasive adenocarcinoma. Seventy percent of IPMNs arise in the pancreatic head and up to 10% involve diffusely the entire gland[3].

HISTOLOGY

IPMNs are divided into 3 groups according to the degree of cyto-architectural atypia: adenoma or low-grade dysplasia, borderline or moderate dysplasia and *in-situ* carcinoma

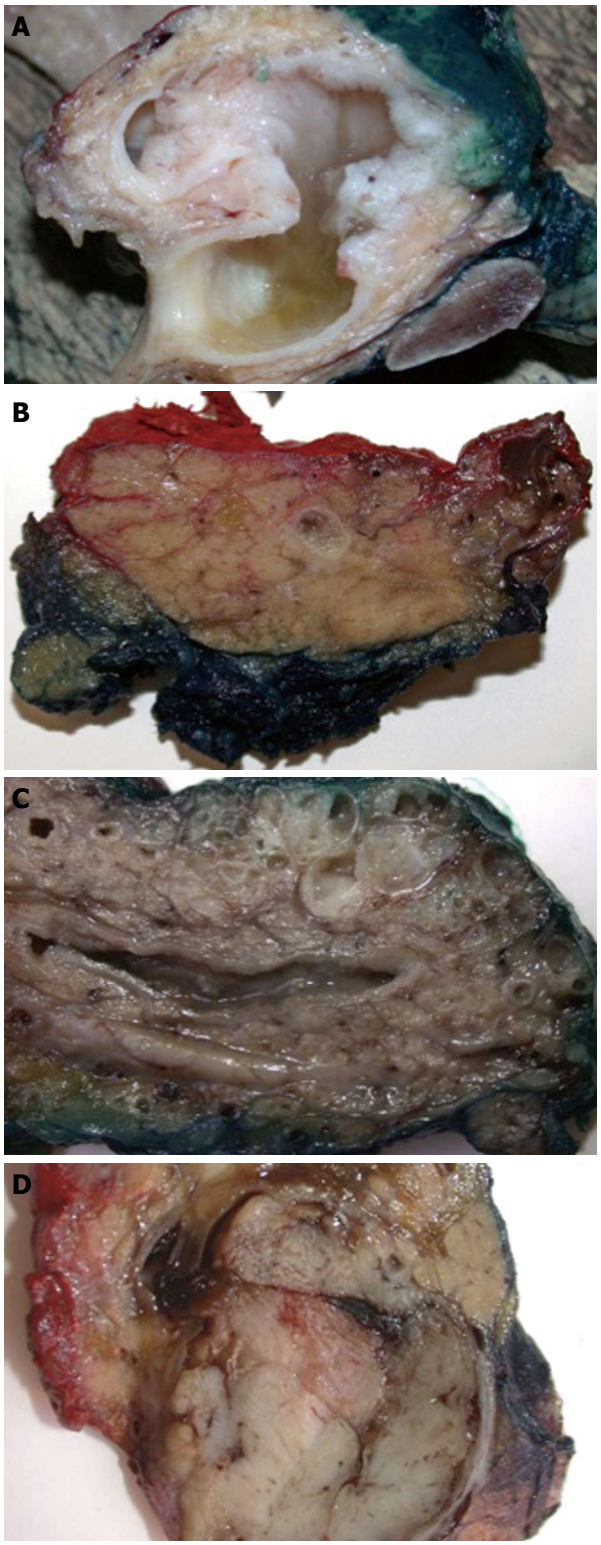

Figure 1 Variation in gross appearance of intraductal papillary-mucinous neoplasm. A: Intraductal papillary-mucinous neoplasm (IPMN) involving the main pancreatic duct with copious mucus and prominent intraductal tumor proliferation causing marked dilatation of the Wirsung and Santorini ducts; B: IPMN of the main duct characterized by subtle granularity of the duct wall, little grossly visible mucin and minimal duct dilatation; C: IPMN involving clusters of dilated and mucin-filled branched ducts. Note mild distension and mucinous content of the main pancreatic duct; D: Distension of a branch duct by solid tumor tissue of an oncocytic-type IPMN.

or high-grade dysplasia[4]. Similar to the adenoma-carcinoma sequence in colonic cancer, these three groups are thought to reflect neoplastic progression. A further classification is based on the morphology of the neoplastic epithelium (Figure 2)[5]. In gastric-type IPMNs, neoplastic epithelium resembling gastric foveolae forms short finger-like papillae or can be flat, and small pyloric-type glands are often present at the base of these lesions. Long villous projections lined with mucin-rich columnar cells, reminiscent of colonic villous adenoma, are characteristic of intestinal-type IPMNs. Pancreatobiliary-type IPMNs consist of complex arborizing papillae which are lined with cuboidal cells containing little mucin. In oncocytic-type IPMNs, the neoplastic epithelia have abundant eosinophilic cytoplasm but usually little mucin and line the papillae in several layers which are complex and merge into solid aggregates. This rare type of IPMN is regarded by some as a separate lesion ("intraductal oncocytic papillary neoplasm")[6,7], mainly because of the lack of KRAS mutations which are frequent in IPMNs[8,9]. The direction of differentiation in the different types of IPMN is reflected in the expression of mucins. MUC1, a membrane-bound mucin detected in adult pancreas, is expressed in pancreatobiliary-type IPMN while the intestinal type secretory mucin MUC2 is found in intestinal-type IPMN. MUC5AC and MUC6 (gastric mucins) are expressed in gastric-type IPMN. MUC5AC in combination with MUC1 or MUC2 can also be found in pancreatobiliary or intestinal type IPMN respectively[4,5,10].

IPMNs are further subdivided depending on whether they involved the main duct, branch ducts or both. It is common for IPMNs to extend microscopically several centimetres beyond the grossly visible lesions[11].

Invasive adenocarcinoma is present in approximately 35% of IPMN-bearing pancreata and can be of colloid (65%) or intestinal type (15%)[12-15]. The former, also known as mucinous noncystic carcinoma, consists of mucin pools with free-floating clusters of cancer cells, expresses MUC2 but not MUC1 and is usually associated with intestinal-type IPMN[16]. It has a more favourable outcome than tubular adenocarcinoma which is identical to conventional pancreatic ductal adenocarcinoma (PDAC) in terms of histomorphology, mucin profile (MUC1+, MUC2-) and prognosis and is often, but not exclusively, associated with pancreatobiliary-type IPMN[17].

Interestingly, there is significant association between the epithelial type, grade of dysplasia, localisation in the pancreatic duct system and risk and type of associated invasive carcinoma. Gastric-type IPMNs usually present as small lesions in branch ducts, with mild dysplasia and a low risk of associated invasive cancer. In contrast, intestinal and pancreatobiliary type IPMNs are larger lesions that involve the main duct and/or connecting branch ducts, exhibit higher-grade dysplasia and bear a higher risk of being invasive[14,18]. These associations suggest that location of IPMNs in the duct system is not a random event but rather reflects intrinsic biological difference[19]. The associations also concur with the observation that invasive carcinoma is more frequently found in main duct than branch duct IPMNs (42% *vs* 12%)[20-23] which has

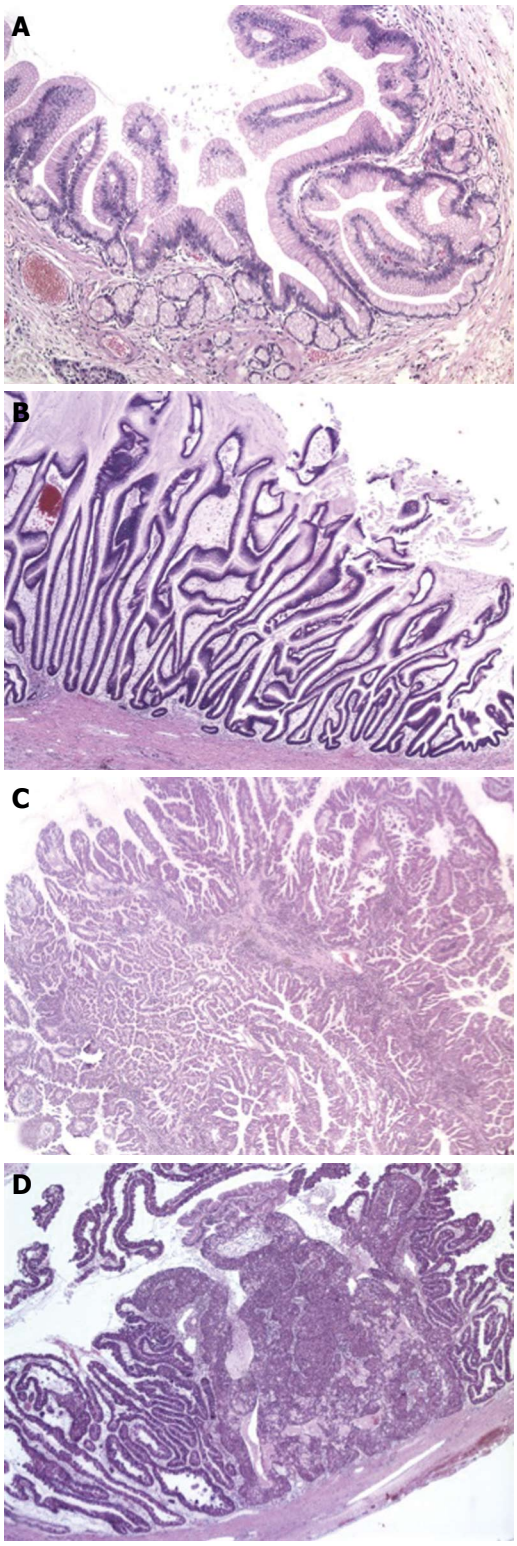

Figure 2 Histological features of different intraductal papillary-mucinous neoplasm types. A: Gastric-type intraductal papillary-mucinous neoplasm (IPMN) with short foveolae-like papillae and clusters of pyloric-type glands (× 50); B: Intestinal-type IPMN characterized by villus-like papillae lined with columnar mucin-rich epithelium (× 25); C: Pancreatobiliary-type IPMN consisting of complex arborizing papillae lined by severely dysplastic epithelium (× 25); D: Oncocytic-type IPMN showing complex papillae and formation of solid areas (× 25).

important clinical implications and shaped the current guidelines for the management of IPMN patients[24].

OTHER MASS-FORMING INTRADUCTAL NEOPLASTIC LESIONS

With the growing awareness of IPMNs, two morphologically similar mass-forming intraductal neoplastic lesions have been recently described. Intraductal tubular neoplasia shares with IPMN the intraductal localisation and associated duct dilatation but differs by its predominantly tubular growth pattern and overall more favourable outcome[25-27]. Intraductal tubulopapillary neoplasia forms solid nodular tumors that obstruct dilated pancreatic ducts, is devoid of any visible mucin and exhibits a tubulopapillary growth pattern with high-grade dysplasia[28]. While both entities are supposedly unrelated to IPMN, a possible link between intraductal tubular adenoma and gastric-type IPMN has been suggested[29].

MOLECULAR BIOLOGY AND GENETICS

Multiple studies have investigated whether the difference in behavior between IPMN and PDAC is reflected in distinctive genetic aberrations. While activating mutation of KRAS is an early event in IPMN development, a significant proportion (14%-69%) of these lesions harbor the wild-type gene[30-33], suggesting that alternative ways of stimulating the Ras-Raf-MEK-MAP kinase pathway are used[34]. The reported frequency of inactivation of P53, P16 and SMAD4/DPC4 varies greatly between reports and depends on the degree of dysplasia of the lesion[35,36]. Overall, however, inactivation of SMAD4/DPC4 appears to be significantly less common in IPMN compared to PDAC[37,38]. IPMNs of patients with Peutz-Jeghers syndrome harbor germline mutations of the *STK11/LKB1* gene and somatic mutation is an uncommon finding in sporadic IPMN[39]. *PIK3CA* is the only gene so far that is mutated in some IPMNs but not in PDAC[40].

Recent global genomic analyses confirm the gradual accumulation of chromosomal imbalances (losses more than gains) in IPMNs in parallel with increasing grades of dysplasia while the average fractional allelic loss appears to be lower compared to PDAC[41,42]. Whereas some chromosomal losses (5q, 6q, 11q) are more frequent in high-grade dysplastic or invasive IPMNs than PDAC, others (8p, 15q, 18q, 22q) occur with similar frequency in both[41-44].

Large-scale gene expression profiling studies of IPMNs reveal up- or down-regulation of numerous genes that are also differentially expressed in PDAC and therefore either relate to early events in carcinogenesis or functions that are common to most cancers[45,46].

Aberrant methylation is common in IPMNs and may contribute more to tumor suppressor gene inactivation than mutational events. It increases in prevalence with grades of dysplasia and is largely completed prior to the transition into invasive carcinoma[47,48]. Invasive IPMNs have multiple methylated genes which are related to cell cycle control (*p16, p73, APC*), DNA repair (*MGMT, hMLH1*) and cell adhesion (*E-cadherin, claudin 5, TSLC1/IGSF1*)[47,49].

Most (non-)invasive IPMNs are microsatellite stable and normally express mismatch repair genes[50,51]. Only a single case of high-level microsatellite instability has been reported in a patient with proven Lynch syndrome[52].

Recently, a large number of other pathways and molecular markers have been investigated. Wnt signalling and DNA damage checkpoint pathways, sonic hedgehog and telomere shortening appear to be aberrant in a proportion of IPMNs, however, further studies are awaited to clarify the significance of these findings[53-56].

CLONALITY, MULTIFOCALITY AND FIELD-DEFECT

Meticulous examination of pancreatic specimens with IPMN demonstrated that up to 32% of cases contain multiple apparently discontinuous lesions which often harbor different KRAS mutations[57-59]. In addition, KRAS mutation and X-chromosomal inactivation studies revealed that up to 80% of IPMNs are poly- or oligoclonal in origin[59-61]. This indicates that the majority of IPMNs can be considered as the result of fusion of two or more independent monoclonal precursor lesions. Multicentric or "field" cancerisation as the basis of IPMN development is further supported by the detection of genetic abnormalities (e.g. monosomy of chromosomes 6 & 17) in morphologically normal duct epithelium lining unremarkable or slightly dilated ducts and in adjacent unequivocal IPMNs[43,61]. FISH analysis demonstrated that within these morphologically normal duct epithelia, cells harboring monosomy 6 or 17 were admixed with cells of a normal karyotype[43]. Hence, IPMNs are not sharply delineated but rather surrounded by a grey zone, an area of as yet unknown extent, containing a mixed population of epithelial cells with or without genetic aberrations. Meanwhile, these findings have been corroborated by the increased prevalence of low-level aberrant methylation in morphologically normal duct epithelium of pancreata from IPMN patients[47].

These observations have important implications. Firstly, they indicate that morphology does not allow accurate identification of epithelial cells with early genomic aberrations. Secondly, the morphologically unremarkable cell populations that harbor genomic alterations could be responsible for local tumor recurrence after partial pancreatectomy with clear margins. Recent reports on concomitant but topographically separate PDAC in 9% of patients followed-up for branch duct IPMN, also point at a field-defect[12,62-64]. IPMNs are therefore not only precursor lesions of invasive carcinoma but also markers of unstable duct epithelium that is at higher risk of carcinogenesis. The underlying molecular mechanisms are, however, as yet unknown and whether these concomitant cancers develop from (small) IPMNs or PanINs is currently not clear[63,65].

ISSUES TO BE ADDRESSED

Practical hurdles

Systematic study of IPMN is hampered by the practical issues related to the establishment of large series that adequately represent the inter- and intratumor heterogeneity of IPMNs in terms of dysplasia, epithelial type and main or branch duct involvement. Because of the significant association between these different features, it is particularly difficult to assess the significance of each feature individually. Moreover, gastric-type IPMNs involving branch ducts are often underrepresented because of the limited availability of tissue samples from these generally small lesions. Hence, large-scale studies with extensive sampling from different, well-characterized areas are needed to clarify the clinical and biological significance of these features and their mutual relationships.

Background duct epithelium

Recent data indicate that morphologically normal duct epithelium adjacent to or away from IPMNs can harbor genomic aberrations[43,47,61]. Systematic analysis of "normal" duct epithelium is therefore required to characterize the molecular nature and extent of the putative field-defect. This will provide information regarding the development and natural history of IPMNs and is likely to have important implications for patient management. For instance, the current practice of guiding the extent of surgery by intra-operative microscopic examination of the resection margin may need reconsideration[4]. In addition, the presence of molecular abnormality in morphologically unremarkable background duct epithelium could possibly allow risk stratification of individual patients in terms of future development of IPMN recurrence or concomitant PDAC.

Relationship with pancreatic intraepithelial neoplasia

One key unanswered question remains that of the relationship between IPMN and pancreatic intraepithelial neoplasia (PanIN). Both are intraductal precursor lesions of invasive adenocarcinoma, progress through a sequence of increasingly severe dysplastic features and share certain molecular aberrations[66-68]. PanINs are usually incidental microscopic findings that involve small branch ducts whereas IPMNs generally produce gross lesions that are manifest clinically or on imaging. However, there is considerable histological overlap, making microscopic distinction often impossible and resulting in a low interobserver agreement, even when using the consensus definitions[69]. According to the latter, distinction is based on size, with lesions < 5 mm regarded as PanINs and those > 10 mm deemed to be IPMNs[70]. This definition has two main disadvantages. Firstly, it obviously leaves a grey area for lesions measuring between 5 and 10 mm in size. Secondly, as it seems reasonable to presume that IPMNs do not ab initio reach a size of 10 mm, adherence to the consensus definition effectively precludes the study of IPMNs at an early stage of development. Interestingly, Shi *et al*[71] recently introduced the notion of "incipient IPMNs" which they defined as morphologically typical IPMNs measuring 5 to 10 mm in size. Systematic reporting of the putative early IPMNs as PanINs bears the risk of obfuscating the true relationship between both lesions.

The closest relationship seems to exist between gastric-type IPMN and lower-grade PanIN which share morphological features, the mucin profile and location within branch ducts. PanINs have been reported to frequently occur next to gastric-type IPMNs[14,72] and both lesions frequently co-exist in patients with a family history of PDAC[71,73,74]. These similarities and co-existence of both lesions suggest they may be aspects of the same disease, whereby low-grade PanINs would represent "small gastric-type IPMNs" and the latter a focal accentuation of an essentially diffuse disease[72].

Animal models

Several genetically engineered mouse (GEM) models currently exist in which PanIN and PDAC are faithfully reproduced[75,76]. A model for mucinous cystic neoplasia of the pancreas, a third known precursor of pancreatic cancer, has been described recently in a GEM model characterized by concomitant expression of $KRAS^{G12D}$ and haploinsufficiency of SMAD4/DPC4[77]. Furthermore, selective biallelic deletion of the latter in combination with the activated $KRAS^{G12D}$ allele has been reported to produce IPMN-like neoplastic lesions[78]. From the work with various GEM models, a complex picture emerges in which the sequence as well as the context in which the same overall spectrum of critical mutations occurs, determining the ensuing pathology[77]. Common to the pathways of different precursor lesions of pancreatic cancer is the initiating event of KRAS mutation with formation of early PanIN-lesions. Depending on the subsequent events, e.g. mutations of P53, P16 or SMAD4/DPC4, progression occurs along the same pathway and higher-grade PanINs develop, or, diversion into a different pathway leads to cystic neoplasia such as the mucinous cystic neoplasm or, possibly, IPMN. In particular, the timing of SMAD4/DPC4 mutation seems to determine which of the pleiotropic effects of this event will be exerted on the evolving precursor neoplasm[77,78]. These observations underscore the limitations of our largely static view of IPMN so far and the need for further development of a GEM model that recapitulates both the clinicopathological features of IPMN and the particular kinetics of this route of carcinogenesis. Through careful comparison with human IPMN, it will allow preclinical testing of novel risk stratification markers and treatment strategies and may provide the rationale for refined follow-up protocols.

CONCLUSION

IPMN is a clinically and morphologically distinct precursor lesion which offers a unique opportunity to study pancreatic carcinogenesis. Further molecular characterization and animal models of IPMN will further clarify the development and progression of this lesion and may provide clinically useful markers for early detection and risk stratification of patients affected by IPMN.

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TOPIC HIGHLIGHT

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Population-based epidemiology, risk factors and screening of intraductal papillary mucinous neoplasm patients

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Abstract

Intraductal papillary mucinous neoplasm (IPMN) was first recognized in the 1980s with increasing publications over the last decade as the incidence increased sharply, especially at tertiary-care referral centers. Population-based studies have estimated the age and sex-adjusted cumulative incidence of IPMN to be 2.04 per 100 000 person-years (95% confidence interval: 1.28-2.80). It is now understood that IPMN can be classified anywhere along the spectrum of the adenoma to carcinoma sequence and often harbors mutations in genes such as KRAS early in the disease process. Many patients are diagnosed incidentally after imaging of the abdomen for other diagnostic purposes. Patients that present with a history of symptoms such as pancreatitis and abdominal pain are at high risk of harboring a malignancy. Clinicopathologic features such as involvement of the main pancreatic duct, presence of mural nodules, and side branch disease > 3.0 cm in size may indicate that there is an underlying invasive component to the IPMN. In addition, the incidence of extra-pancreatic neoplasms is higher in patients with IPMN, with reported rates of 25% to 50%. There are no current screening recommendations to detect and diagnose IPMN but once the diagnosis is made, screening for extrapancreatic neoplasms such as colon polyps and colorectal cancer should be considered. Surgical resection is the recommend treatment for patients with high-risk features while close observation can be offered to patients without worrisome signs and symptoms of carcinoma.

Key words: Intraductal papillary mucinous neoplasm; Incidence; Prevalence; Risk factors; Screening

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INTRODUCTION

The first report of intraductal papillary mucinous neoplasm (IPMN) was made in 1982 by Ohasi *et al*[1] who described 'mucin-producing' pancreatic neoplasms in four patients. In an effort to identify the presence of IPMN prior to 1982, a single hospital-based study was undertaken

by Tollefson and colleagues[2] at Mayo Clinic. They evaluated slides from 84 of 4000 patients with pancreatic cancer who were treated from 1960 to 1980. All patients had a histology report with terms such as "mucinous', "cystic", or "papillary". The diagnosis of IPMN was made in 21 of these 84 patients, implicating that IPMN was present prior to 1982, but went unrecognized.

Intraductal papillary mucinous neoplasm was not established as a distinct entity until more than a decade after its identification. Prior to that, a number of terms (e.g. mucinous ductal ectasia, intraductal papillary mucinous tumor (IPMT), mucin-secreting neoplasm, *etc.*) were used to describe these lesions in the literature, leading to extensive variability in terminology when reporting the disease. This issue was partially resolved in 1996, when the World Health Organization (WHO) classified cystic mucin-producing tumors and fully resolved in 2000 when a revision differentiated between IPMN and mucinous cystic neoplasm (MCN). Strict diagnostic criteria were proposed for each disease type. There are three types of IPMN (main duct, branch duct, and mixed), and the WHO has recommended classifying these lesions histopathologically as benign, borderline, or invasive carcinoma.

Further clarification for the diagnosis, management, and prognosis of the disease was achieved in 2004 after consensus conferences were held by experts at Johns Hopkins University[3] and by members of the International Association of Pancreatology who convened in Sendai, Japan[4]. The criteria established at these conferences have dictated the contemporary definition, evaluation, and management of IPMN.

POPULATION-BASED EPIDEMIOLOGY

Over the last two decades, there has been an increase in the number of publications related to IPMN. Many of these reports suggest that the frequency of IPMN is increasing, an observation that coincides with the increasing use and availability of computed tomography (CT) and other abdominal imaging modalities[5-7]. The vast majority of these studies have dealt with the diagnosis and operative outcome of affected patients rather than the epidemiology or natural history[8-10]. Given that there are no 'screening' protocols for IPMN to-date (not deemed necessary because of its rarity), available data on incidence and prevalence is primarily based on extrapolation from single tertiary health care center reports. The underlying assumption is that all patients with IPMN in that population were treated at the designated hospital. Therefore, there is an obvious risk of under-estimating the incidence or prevalence of IPMN since only patients who are symptomatic or receive an incidental diagnosis receive clinical attention.

Cognizant of the above issues, we reported the first and only population-based study of the incidence and prevalence of IPMN[11]. The study population encompassed Olmsted County, Minnesota, which is served by a unified healthcare system. The goal was to take advantage of the Rochester Epidemiology Project (REP)[12], a unique medical records-linkage system that encompasses the care delivered to residents of Olmsted County, Minnesota. The REP combines clinical documentation of patients seen at Mayo Clinic with those obtained by other providers in the county. The REP is therefore able to provide incidence data for almost any condition and can also support population-based analytic studies of diseases and outcomes.

In our study, the multi-linked REP database was queried for all in- and out-patient visits, autopsy reports, and nursing home care using the relevant International Classification of Diseases (ICD) codes. Patients with a clinical diagnosis of IPMN made on imaging, endoscopy (including endoscopic ultrasound and/or endoscopic retrograde pancreatography), or pathological assessment were included. Pathological slides of all identified cases were examined by two expert pathologists. Incident cases were identified between January 1, 1984, and December 31, 2005, among residents of Olmsted County aged 20 years or older.

INCIDENCE AND PREVALENCE

The age and sex-adjusted cumulative incidence of IPMN in Olmsted County was 2.04 per 100 000 person-years [95% confidence interval (CI): 1.28-2.80]. The incidence seemed to increase with time (0.3 per 100 000 during 1984-1985 to 4.5 per 100 000 person - years during the period of 2001-2005), but the number of annual cases remained low. The point prevalence, on December 31, 2005, was 25.96 cases per 100 000 persons (95%CI: 14.5-37.3); however, this increased to 99 cases per 100 000 (95%CI: 54-143) in those older than 60 years. The median age at the time of diagnosis was 73.1 years (range 41-92 years), and the majority of patients were asymptomatic and received the diagnosis incidentally.

While the data suggests an increase in the incidence of IPMN over time, it is important to distinguish between a rising diagnosis and treatment of the condition with an accumulation of cases at specialist centers, as opposed to a true rise in incidence[13]. Our data suggests a low incidence in the county which appears to be on the rise. The data, however, does not depict an 'epidemic'. Further epidemiologic studies may help resolve the true change in pathological behavior.

Recently, Simons and colleagues[14] investigated national resection rates and survival for malignant IPMN between 1988 and 2005 using the nationwide database, Surveillance Epidemiology and End Results (SEER). The United States Census data were utilized to investigate age-adjusted statistics. A total of 1834 patients were identified with malignant IPMN from the database. Of those patients, 54% did not undergo surgery, and the remaining patients had operative resection. The age-adjusted incidence for malignant IPMN varied over the study period varied starting at 0.48 per 100 000 in 1988 to 0.29 per 100 000 in 2003; whereas, the number of patients undergoing resection rose significantly ($P = 0.001$) from 5.8% in 1998 to 14.8% in 2003, the highest rate of resection being 16% in 2001. The median survival of resected and non-resected patients

was 16 and 3 mo respectively. The authors concluded that detection of malignant IPMN is decreasing but earlier detection is contributing to increasing resection rates.

In another epidemiologic study using the California Cancer Registry, a segment of SEER, from 2000-2007, Le *et al*[15] reported over 15 000 cases of pancreatic cancer. Of those cases, 880 patients were diagnosed with mucinous tumors, but only 43 were diagnosed with IPMN. The hazard ratio of IPMN in this population was 0.19 (0.10-0.35). Le concluded that IPMN is rare, and if resected, had a statistically better prognosis than pancreatic adenocarcinoma. Incidence or prevalence data were not reported.

Yoon and colleagues[16] investigated the frequency of cystic pancreatic neoplasms by exploring patient records from 20 university-teaching hospitals between 1993 and 2005. All diagnoses were confirmed surgically or were biopsy-proven. They found IPMN to be the most commonly reported cystic neoplasm, 436 of 1064 patients. Contrary to our findings, only 32% of their patients were asymptomatic and only 13% were diagnosed incidentally. One of their expected findings was that asymptomatic patients had a lower risk of harboring malignancy.

Most of the epidemiologic studies outlined above share the limitations of population-based analyses including the lack of independent histologic review of specimens, variable sources of reporting and diagnostic methods, and broad staging criteria (that is, SEER summary staging instead of American Joint Committee on Cancer staging methods). However, it appears that the incidence of IPMN is rare with estimates between 0.48-2.04 per 100 000 persons. There is no conclusive evidence that IPMN is rapidly increasing in the general population but reported data[6] does suggest an increase of patients seen at tertiary health care centers with the disease.

RISK FACTORS

Reports on risk factors for IPMN are also rare in the literature. Potential risk factors include chronic pancreatitis. In an attempt to see if patients with chronic pancreatitis were at risk for IPMN, Talamini and colleagues[17] reported a long-term study of patients diagnosed with chronic pancreatitis between 1981 and 1998. A total of 476 patients were identified, 93 of whom had chronic obstructive pancreatitis and 46 had biopsy-proven IPMN. The two groups were compared with respect to age, gender, smoking and alcohol history. The group of patients with IPMN had significantly fewer smokers and consumed less alcohol. They concluded that the IPMN was the cause of chronic pancreatitis in these patients rather than an effect.

No clinical reports have identified any lifestyle (smoking, alcohol, excessive body mass index, *etc.*), geographic, viral, history of exposure (to radiation), or familial link to IPMN and genetic advances remain the only avenue of progress in better understanding the likely causality[18]. The absence of evidence, of course, does not categorically eliminate these factors and one has to accept the paucity of investigations in this arena.

SCREENING OF PATIENTS WITH INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM

While there are no formal recommendations for population-based screening of IPMN, there is a growing body of literature reporting the increased incidence of extrapancreatic neoplasm in patients with IPMN[19-25],suggesting that patients with IPMN should be screened for other neoplasms. Sugiyama *et al*[26] investigated the incidence of non-pancreatic neoplasms in 42 patients undergoing resection for IPMN. They reported a high incidence of neoplasms (48%), particularly malignancies (36%). Colorectal adenomas, adenocarcinomas, and gastric carcinomas accounted for the majority of non-pancreatic neoplasms. In their study, the incidence of non-pancreatic neoplasms and malignancies was significantly higher in patients with IPMN than in patients with pancreatic ductal adenocarcinoma (PC) (11% *vs* 7%).

Similarly, Kamisawa *et al*[22] found malignancies in 35% of patients diagnosed with IPMN, particularly gastric and colonic in origin. The majority (85%) were diagnosed prior to or at the time of the diagnosis of IPMN. Interestingly, three patients with IPMN had also independent PC, and all patients diagnosed with IPMN were found to be of branch-duct type located in the head of the pancreas. Choi *et al*[19] studied 61 patients who underwent operative resection for IPMN and found extra pancreatic neoplasms and malignancies in 39% and 30% of patients, respectively. The majority were discovered preoperatively or at the time of surgery; again gastric and colorectal cancers were the most common. The incidence of extra-pancreatic neoplasms was higher in patients with IPMN than in patients with MCN or PC (39% *vs* 8% *vs* 10% respectively).

These same results were found in an epidemiologic study by Riall *et al*[27] who evaluated 19 000 patients from the SEER database with either sporadic PC (95%) or invasive IPMN (5%). In both groups, 10% of patients had one or more extra-pancreatic primary cancers in addition to their primary PC. The most common sites were colorectal (20.1%), breast (19%), prostate (16.6%), urinary system (11.1%), and lung (9.8%). In contrast to the previous studies, gastric cancer was on found only in 1% of patients with invasive IPMN. A similar rate was found for esophageal cancer. Again, the majority (86%) were diagnosed prior to the diagnosis of invasive IPMN. Although the incidence of additional primary malignancies in this population-based study was not as high as previously reported in smaller studies, the findings are still significant and comparable to the incidence seen in patients with sporadic PC, warranting the surveillance of patients with IPMN. Interestingly, these patients are not only at higher risk for other primary cancers, but they are also at a greater risk for a PC even after margin negative resection for benign (non-invasive) disease[28].

In our recent study[11] evaluating the presence of extra-pancreatic neoplasms in patients diagnosed with IPMN,

the proportion of patients having any diagnosed prior to or coincidentally with diagnosis of IPMN was 52%, compared with 36% in PC patients and 43% in the general referral population at Mayo Clinic in Rochester, Minnesota. Benign neoplasms, most frequent in the IPMN group, included colonic polyps (24%) and Barrett's esophagus (4%). Additionally, non-melanoma skin (7%), breast (5%), prostate (5%), colorectal cancer (4%), and carcinoid tumors (1%) were the most common malignant neoplasms observed. This study differs from all others in that it examines the frequency of extra-pancreatic neoplasms in patients with all stages of IPMN, independent of whether they were operatively resected or followed with observation and surveillance alone.

Our findings support the previous reports that patients with IPMN are at an increased risk for having extra-pancreatic neoplasms (benign and malignant), diagnosed before or coincidentally to their diagnosis of IPMN when compared to matched groups of patients with PC and general referral controls. Based on our data, we recommend that all patients with a new diagnosis of IPMN undergo a screening colonoscopy to detect adenomatous polyps or colorectal cancer. An upper endoscopy to rule out Barrett's esophagus should be considered in patients with symptoms of gastroesophageal reflux or dysphagia.

CONCLUSION

The incidence of IPMN in the population is low but the frequency of patients diagnosed with IPMN is increasing at tertiary care facilities. These patients are at an increased risk of developing benign or malignant neoplasms, especially colorectal in orgin. Based on available reports, we recommend that all patients diagnosed with IPMN undergo a screening colonoscopy. A screening upper endoscopy should be reserved for patients with upper gastrointestinal symptoms.

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TOPIC HIGHLIGHT

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Intraductal papillary mucinous neoplasm and the pancreatic incidentaloma

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Abstract

Asymptomatic pancreatic lesions (APL) are a commonly encountered problem in today's pancreatic surgical practices. Current literature regarding etiologies and incidence of APLs, particularly intraductal papillary mucinous neoplasm (IPMN), is presented. APLs constitute a wide spectrum of pathology (solid/cystic, benign/premalignant/malignant) but, overall, IPMN is now the most common diagnosis. The Sendai Guidelines and their function as a basis for risk stratification in branch duct IPMN are presented. The importance of traditionally analyzed cyst characteristics including size, presence of mucin or nodules and cyst fluid aspirate as indicators of malignancy is emphasized, noting also the potential correlation of main duct dilatation, thickened septae and elevated cyst fluid CEA with increased risk of malignancy. Current complication rates after resection of APLs are reviewed and found to be generally equivalent to those for symptomatic resections. A potential multidisciplinary treatment strategy is offered considering the costs of surgery versus repeated imaging or follow up endoscopy for these lesions. The decision for intervention is ultimately based on the Sendai Guidelines in the context of the individual patient.

SCOPE OF THE ISSUE

Asymptomatic pancreatic lesions (APL), first described in 2001 as "incidentalomas"[1], are now known to comprise between 6% and 23% of pancreatic resections for any cause[2-4]. Largely attributed to increasing numbers of radiological studies obtained, the prevalence of cystic APLs on axial imaging is now reported to be between 1.2% and 2.6%[5,6]. Additional lesions can be identified from abnormal blood work or endoscopy evaluations[2,3,7]. APLs are noted most commonly during the evaluation of genitourinary complaints, chest pain or screening/cancer surveillance tests[3,4].

Up to half of such lesions are solid[3] and the vast majority of these are either malignant or at least premalignant. Traditional pancreatic resection remains the mainstay of treatment as it does for similar lesions which are symptomatic. On the other hand, determining the best management strategy for cystic APLs has been complicated because not all lesions have malignant potential and accurate preoperative determination of that threat remains problematic. Given the imperfect diagnostic information available, surgeons must therefore weigh up the risks and benefits of performing a potentially morbid operation for a perhaps benign condition.

Table 1 Comparison of asymptomatic pancreatic lesions diagnoses and operative management (%)[a]

	Winter *et al*[2]	Spinelli *et al*[6]	Sachs *et al*[3]	Fernández-del Castillo *et al*[8]	Bruzoni *et al*[4]
Diagnosis					
IPMN	35.6	24.5	17	27	9
MCN	17	32.6		28	7
SCN	[b]	20.4	14	16.6	12
Pseudocyst	0	-		3.8	-
Adenocarcinoma	18.6	6.1		2.5	30
Neuroendocrine	9.3	8.2	13	-	19
Other	19.8	8.2		10.2	14
No diagnosis	N/A	N/A		11.5	9
> 1 diagnosis	-	-	6.4		
Operation					
Whipple	100%[c]	41	29.1	32	26.4
Distal panc		31	38.2	23	22.8
Central panc		0	6.4	11.5	5.3
Total panc		0	2.7	6.4	3.5
Enucleation		22	4.5	2.5	0
Pseudocyst dr.		0	0	0	0
Exp laparotomy/other		6	19.1	2.5	0
No surgery		N/A	N/A	21.8	42

[a]Note that some studies include cystic asymptomatic pancreatic lesions only, whereas others include both solid and cystic; [b]MCN/SCN included together here; [c]Study included only Whipple's by design. IPMN: Intraductal papillary mucinous neoplasm; MCN: Mucinous cystic neoplasms; SCA: Serous cystadenomas.

ETIOLOGIES OF ASYMPTOMATIC PANCREATIC LESIONS

Incidentally-identified cystic lesions of the pancreas are most commonly intraductal papillary mucinous neoplasms (IPMN), mucinous cystic neoplasms (MCN), serous cystadenomas (SCA), true cysts or pseudocysts as well as a variety of other rare etiologies. In about a tenth of incidental lesions noted radiographically or endoscopically, no definitive pathological diagnosis is obtained[3,8]. Of 212 consecutive pancreatic cystic lesions in one series, 37% were incidental[8]. Pseudocysts, not surprisingly, comprised only 4% of the asymptomatic group. MCN (28%) and IPMN (27%) were the most common diagnoses of resected APLs. However, a substantial number (17%) were ultimately found to be a benign SCA, drawing attention to the limitations in our preoperative evaluation of these patients.

IPMN, which develops along a spectrum of epithelial dysplasia from non-invasive to frankly malignant, is a common diagnosis in this scenario. Two primary varieties occur: Main-Duct (MD; dilatation of the main pancreatic duct) or Branch-Duct (Br; dilatation of side branches in the absence of main-duct dilatation). A third type called mixed-variant is less frequently seen and involves elements of both MD and Br histology[9]. In a series from Johns Hopkins which includes both solid and cystic lesions[2], IPMN (mostly non-invasive) constituted 35.6% of incidental pancreatic head lesions. A full 1/3 of their IPMN cases had a malignant diagnosis (high-grade dysplasia or invasive adenocarcinoma) though, of note, no distinction was made between MD IPMN and Br-IPMN. However, incidental cases had a disproportionally lower stage compared to their symptomatic counterparts, equating to an improved survival by 10 mo. The authors acknowledge the different proportion of favorable pathology and the effect of lead-time bias on the incidental group[2]. Lahat *et al*[5] expanded this idea to examine APLs situated throughout the gland. Of 465 pancreatic resections in their series, 13.5% were for incidental lesions. The percentage of malignant diagnoses in this group (34.3%) was about half that for the symptomatic cohort. IPMN was again the most common diagnosis in the incidental group (23.4%) whereas it constituted only 9% of the symptomatic cases where adenocarcinoma (PDAC) was by far the most common diagnosis[5]. Eighty seven percent of their incidental IPMNs were classified as adenomas or borderline lesions *vs* 59.4% in the symptomatic group (Table 1). From our own practice over a recent 5-year period, resected APLs were most commonly IPMN (17%), SCA (14%) and neuroendocrine tumors (13%). Overall, including both solid and cystic APLs, 71% were malignant or pre-malignant tumors. Of cystic APLs, a full one-third were IPMN, 26% SCA and 12% MCN. The rate of invasive malignancy among these lesions was 1.7% but, including lesions with high-grade dysplasia, the total malignancy rate for cystic APLs was 10.5%[3]. Symptomatic patients resected during the same time-period were more likely to have pancreatitis, pseudocysts and benign strictures.

As emphasized elsewhere in this collection, the distinction between MD-IPMN and Br-IPMN is a crucial one given their different rates of progression to malignancy (63% *vs* 15% respectively)[10]. Both forms are frequently found incidentally (Figure 1). Of 145 patients with resected Br-IPMN, 40% were identified incidentally and there was no difference in malignancy between symptomatic and incidental lesions[11]. This review, representing the combined efforts of the Massachusetts General Hospital and the University of Verona, provided important justification of the Sendai consensus guidelines (below). Five years survival data among this large sample of resected Br-IPMN

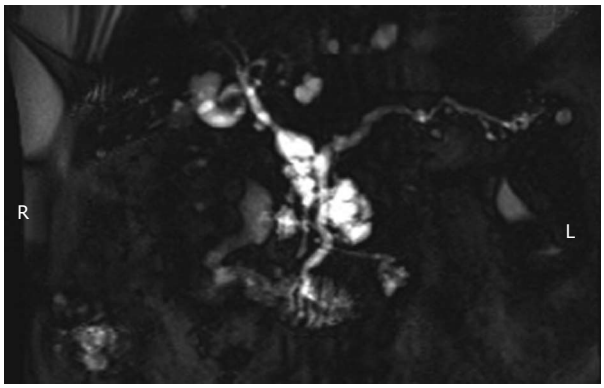

Figure 1 MRCP demonstrating intraductal papillary mucinous neoplasm in the head of the pancreas and uncinate, with dilated main duct > 6 mm, and multiple dilated side branches, likely representing mixed-type intraductal papillary mucinous neoplasm.

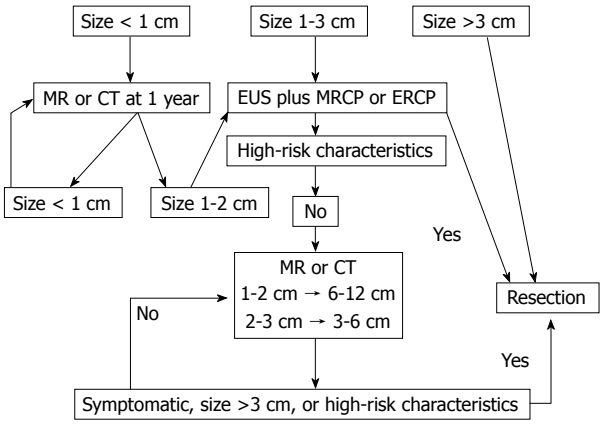

Figure 2 Management algorithm for intraductal papillary mucinous neoplasm (branch duct)[12]. CT: Computed tomography.

differed significantly for non-invasive (100%) compared to invasive cases (63%)[11], underscoring the fundamental issue with Br-IPMN; that is, they are significantly less likely to become malignant compared to MD-IPMN. Yet, waiting to operate until the Br-IPMN has become malignant significantly diminishes survival. Thus, it is critical to identify which Br-IPMN lesions are more likely to progress.

From the accrued literature, we can conclude that incidental lesions may be either solid or cystic. Solid tumors generally require resection just as if they were symptomatic. The majority of incidental cystic lesions are mucinous with both IPMN and MCN occurring frequently. However, SCAs still comprised a relevant proportion of resections. Overall, the proportion of malignant cases in this group was low but premalignant lesions were quite common. It is critical to distinguish between MD-IPMN and Br-IPMN because of their variable aggressiveness.

SENDAI GUIDELINES

Since the initial reports of APLs, considerable effort has been devoted to the study of pancreatic cystic lesions and their management, culminating in 2006 with the publication of the Sendai Consensus Guidelines for the management of mucinous neoplasms of the pancreas[12]. This important position paper addressed the distinction between branch-duct and main-duct IPMN and further highlighted the need for appropriate preoperative classification. These guidelines recommend traditional resection including lymph node dissection for all MD-IPMN and MCN in reasonable surgical candidates. Resection is also recommended for Br-IPMN that is symptomatic, > 3 cm, have mural nodules or demonstrate cyst-aspirate cytology which is positive for malignancy[12]. Algorithms for follow-up of unresected IPMN were also provided, calling for computed tomography (CT), MRCP and/or EUS at intervals depending on size (< 1 cm, yearly; 1-2 cm, 6-12 mo; > 2 cm, 3-6 mo). Development of symptoms, nodules, cyst size > 3 cm or main duct dilatation > 6 mm during observation would then prompt consideration for resection. In the absence of change over a 2-year period, the interval between reevaluation may be lengthened. Those patients whose resected lesions are benign MCNs do not warrant follow-up but those with IPMN (particularly malignant) do have a risk of recurrence and should be reimaged yearly[12]. See Figure 2 for summary of guideline recommendations.

Despite the presence of these guidelines, medical and surgical pancreatologists continue to struggle with questions of what is really the best strategy for IPMN; specifically, which cystic lesions require resection and what follow-up is required for those patients undergoing resection as well as those who are observed. Subsequent work has augmented the body of knowledge on cystic lesions since Sendai. For instance, Tanno *et al*[13] have found that patients with a main pancreatic duct > 6 mm are more likely to demonstrate increasing cyst size or nodule development during follow-up and propose that main-duct diameter may help us predict which lesions will ultimately progress[13]. Among patients with solid or cystic APLs, elevated LFTs have also been found to correlate with the presence of malignancy[3]. Application of the Sendai guidelines has a negative predictive value of approximately 85%, indicating that several malignancies would be missed without further risk stratification[14].

While resection is generally recommended for premalignant lesions, the risks of the intervention must be weighed against the chance of progression to malignancy. Strict adherence to guidelines is not practically possible and reason dictates that a more flexible approach should be tailored to the individual patient's circumstances. For example, an elderly patient with multiple comorbidities and an asymptomatic cystic lesion, even if MD-IPMN, may not be best served by a pancreatectomy. The difficulty is that we still do not know precisely the rate at which progression to malignancy will occur - either for the overall population or for any given patient who harbors an IPMN[15].

OUTCOMES

To help evaluate the benefit of resection for APLs, we must consider the necessary operations and their associated outcomes. Of studies incorporating lesions through-

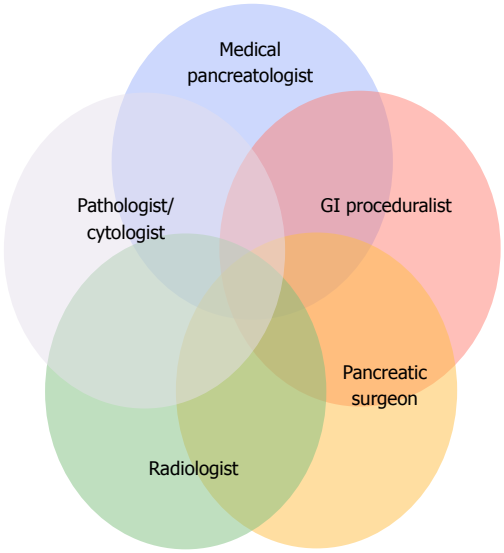

Figure 3 Multidisciplinary components in the management of pancreatic cystic neoplasms.

out the gland, APLs have accounted for 9%-31% of all pancreaticoduodenectomies and 22%-38% of distal resections[3,5,8] in focused pancreatic surgical practices.

Most groups report equivalent rates of overall morbidity (roughly 50%)[2,5,11] in patients with symptomatic and asymptomatic lesions. We had a 28% overall morbidity rate in our APL resections without any mortality[3]. Pancreatic fistula rates have varied by study depending in part on the inclusion or exclusion of distal resections and specific definitions employed. Rodriguez *et al*[11] reported a 17% fistula rate equivalent with their symptomatic patients and, in our series at BIDMC, clinically relevant (ISGPF grade B and C) fistulas occurred in 9%[3]. Winter *et al*[2] and Lahat *et al*[5] demonstrated higher fistula rates for their asymptomatic patients (25% and 18.4% *vs* 10.5% and 8.5% respectively). Important information is also available on the rarely reported outcomes of development of exocrine insufficiency (22%) and new or worsened diabetes (28%) in patients undergoing resection for benign Br-IPMN[11].

Comparison of survival among symptomatic and asymptomatic patients must be cautiously interpreted. A difference in survival can be attributed to a different breakdown of diagnoses (i.e. higher proportion of PDAC) in each group, as is seen and acknowledged by the Hopkins group[2]. Lahat *et al*[5] were able to compare survival specifically for their mucinous tumors; although median survival was not yet reached, there was a trend toward improved survival in the incidentally-identified IPMN and/or MCN (94%) compared to the symptomatic lesions (68%)[5].

In today's practice environment, cost-effectiveness must also be considered as an outcome. Costs of long-term surveillance must be considered against the immediate costs of a high-acuity operation. This issue is not yet well delineated. In our recently published paper, patients with APLs were submitted to a median of 3 radiological tests prior to proceeding to surgery[3]. EUS and associated biopsy/FNA/cyst fluid analysis adds considerable additional cost. In IPMN cases, patients require follow-up even if they have a resection initially to identify possible recurrence. Das *et al*[16] conducted a decision analysis comparing surgery for all patients to follow-up for all to a cohort of intervention guided by EUS/cyst fluid analysis and subsequent risk stratification. Risk stratification-based treatment demonstrated the highest quality added life years and cost-effectiveness. Lastly, it is difficult to measure the true cost of a high-acuity operation with potential additive costs for complications for what turns out to be benign disease (i.e. an unnecessary resection) or, alternatively, the psychological burden and cost for a patient submitted to repeated scans and lengthy follow-up for a potentially pre-malignant tumor.

TREATMENT APPROACHES

At our institution, we approach these lesions in a multidisciplinary fashion so that each patient is initially evaluated by a surgeon, a medical pancreatologist and a gastroenterologic proceduralist (Figure 3). Imaging exams are interpreted with dedicated pancreatic radiologists and efforts are made to accrue and evaluate antecedent scans in order to determine the natural history (growth or change of lesion morphology) of the lesion in question. In recent years, we have seen a stark increase in referrals for the evaluation of APLs to the point where they now comprise half of all referrals to our pancreatic surgical practice and nearly a quarter of all our resections[3].

Initial management typically includes treatment of the presenting problem if present. CT angiography of the pancreas is preferred for solid lesions whereas MRI is the primary modality used for follow-up of cystic lesions to best delineate the cyst and its relationship to the ductal system. With previous reports of only moderate sensitivity (69%) and specificity (90%) for EUS/ FNA[8] and unclear utility of cyst fluid analysis, we used EUS infrequently in the past. However, recent work has found EUS to be useful for predicting mucinous lesions by virtue of elevated cyst CEA (> 200 ng/mL)[3,17]. The value of additional biochemical cyst fluid analysis is debatable and we have found that it provides additive value to CEA analysis[18]. Furthermore, in our experience, atypical cytology on FNA was always associated with an ultimately premalignant tumor[3]. Thus, we now utilize EUS more frequently in the evaluation of both solid and cystic lesions. ERCP is rarely required to further evaluate side branch communication with the main duct or perhaps extent of involvement of MD-IPMN.

As solid lesions are much more likely to be malignant, most of these patients will undergo resection assuming they are reasonable surgical candidates. Care should be taken to rule out the rare occurrence of an aberrant splenule within the pancreas. For cystic lesions, we generally ascribe to the Sendai Consensus guidelines, as already mentioned above, and have seen a reversal of the ratio of resection to observation since their adoption. However, each patient's particular circumstances contribute to deci-

sion making. Given the higher risk of malignant transformation, MCNs and MD-IPMN will generally undergo resection with a traditional pancreatectomy including regional lymphadenectomy in suitable surgical candidates. Of note, for multifocal Br-IPMN, we will typically resect the dominant disease if technically possible rather than proceed to total pancreatectomy in order to preserve function. Otherwise, cystic lesions that are < 3 cm, lack mural nodules, thickened septae, ductal obstruction or atypical/malignant FNA may qualify for observation on a case-by-case basis. Subsequent evaluation with MRI and/or EUS is then warranted as described above.

Development of the concerning features delineated above prompts reconsideration for resection. Furthermore, we consider anxiety in some cases to be a significant burden for many patients and have had many so anxious at the prospect of continued observation that they ultimately requested resection instead. This mandates a thorough and balanced discussion of risks and benefits with these patients. Postoperative follow-up is also regularly employed which entails additional imaging and clinical examination for those patients at risk for recurrence (malignant MCN, malignant IPMN, IPMN with retained dysplastic margins or multifocal disease which was not resected as well as other solid neoplasms).

CONCLUSION

APLs are a commonly encountered problem in today's pancreatic surgical practices. IPMN is a frequent cause of the asymptomatic presentation, whether main- or branch-duct. Mucinous lesions generally should be resected due to the risk of malignancy. The Sendai Guidelines are a solid foundation on which to begin risk stratification for Br-IPMN. Aside from cyst size > 3 cm, presence of nodules and cyst fluid aspirate positive for malignancy, others have found main duct dilatation, thickened septae and elevated cyst fluid CEA to correlate with increased risk of malignancy. Complication rates after resection of APLs are generally equivalent to those for symptomatic resections, although some groups report a higher fistula rate. Exocrine and endocrine insufficiency will occur in approximately one-quarter of such resections. Although high-acuity surgery as required for resection of these lesions is costly, so, too, is repeated imaging or endoscopic intervention for follow-up. Ultimately, the Sendai Guidelines should be considered in the context of the individual patient, weighing up their anxiety, comorbidities and cyst characteristics against the risks and benefits of a pancreatic resection.

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TOPIC HIGHLIGHT

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Imaging considerations in intraductal papillary mucinous neoplasms of the pancreas

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Abstract

With the widespread use of cross-sectional imaging, particularly computed tomography (CT) and magnetic resonance imaging (MRI), and the continuous improvement in the image quality of these techniques, the diagnosis of incidental pancreatic cysts has increased dramatically in the last decades. While the vast majority of these cysts are not clinically relevant, a small percentage of them will evolve into an invasive malignant tumor making their management challenging. Mucinous cystic neoplasms and intraductal papillary mucinous neoplasms (IPMN) are the most common pancreatic cystic lesions with malignant potential. Imaging findings on CT and MRI correlate tightly with the presence of malignant degeneration in these neoplasms. IPMN can be classified based on their distribution as main duct, branch duct or mixed type lesions. MRI is superior to CT in demonstrating the communication of a branch duct IPMN with the main pancreatic duct (MPD). Most branch duct lesions are benign whereas tumors involving the MPD are frequently associated with malignancy. The presence of solid nodules, thick enhancing walls and/or septae, a wide (> 1 cm) connection of a side-branch lesion with the MPD and the size of the tumor > 3 cm are indicative of malignancy in a branch and mixed type IPMN. A main pancreatic duct > 6 mm, a mural nodule > 3 mm and an abnormal attenuating area in the adjacent pancreatic parenchyma on CT correlates with malignant disease in main duct and mixed type IPMN. An accurate characterization of these neoplasms by imaging is thus crucial for selecting the best management options. In this article, we review the imaging findings of IPMN including imaging predictors of malignancy and surgical resectability. We also discuss follow-up strategies for patients with surgically resected IPMN and patients with incidental pancreatic cysts.

Key words: Pancreatic neoplasms; Intraductal papillary mucinous neoplasms; Computed tomography; Magnetic resonance imaging

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INTRODUCTION

The diagnosis of incidental pancreatic cysts has increased dramatically in the last decades because of the widespread use of cross-sectional imaging and the technical developments in these techniques that have allowed for faster imaging of the abdomen along with improved spatial and contrast resolution. The prevalence of incidental asymptomatic pancreatic cysts may be as high as 3% and 14%-20% in patients undergoing computed tomography

(CT)[1] and magnetic resonance imaging (MRI)[2,3] respectively. While some studies support that the majority of these cysts are not clinically relevant[4,5], a small percentage of them may evolve into an invasive malignant tumor[5,6]. The differential diagnosis of cystic lesions in the pancreas is broad and includes non-neoplastic lesions (i.e. pseudocyst) and cystic neoplasms [serous cystadenomas, mucinous cystic neoplasms and intraductal papillary mucinous neoplasms (IPMN)]. Mucin-producing neoplasms, including IPMN, have malignant potential and therefore are considered surgical lesions. Thus, accurate characterization of these lesions is crucial for selecting the best management options.

The importance of cross-sectional imaging in the presurgical evaluation of IPMN has been extensively emphasized in the literature[7-14]. The tight correlation between imaging findings and histopathological features of these neoplasms, with further sub-classification based on the location and degree of involvement of the pancreas, provides the basis for including imaging in a decision-making algorithm proposed for the management of IPMN[15].

Follow-up imaging strategies for patients with presumed IPMN have been proposed[15]. However, clear recommendations for imaging follow-up in patients with a pathologically-confirmed diagnosis of IPMN after surgical resection are lacking at the present.

The aim of this article is to review the imaging characteristics of IPMN, with emphasis on the correlation between cross-sectional imaging findings and histopathology, and to review imaging follow-up strategies for patients with a presumed diagnosis of IPMN and for those with pathologically-confirmed IPMN after surgical excision.

CROSS-SECTIONAL IMAGING OPTIONS

CT and MRI are the most commonly utilized non-invasive imaging techniques for assessment of pancreatic cystic lesions. While ultrasound (US) is an excellent technique for demonstration of the internal architecture in these cysts, the presence of air in overlying bowel limits the utility of this technique transabdominally. For this reason and because of the added advantage of direct sampling capability, the use of endoscopic US has proliferated in the last decade for the evaluation of pancreatic cysts.

A dedicated multiphasic, multidetector CT protocol of the pancreas with multiplanar and curved reconstructions is recommended for the presurgical evaluation of pancreatic cysts[14,16,17]. Similar to patients with pancreatic adenocarcinoma[18], this protocol offers accurate information about tumor staging and vascular anatomy.

MRI protocols typically include a combination of T1-weighted, T2-weighted and dynamic contrast-enhanced, fat-saturated T1-weighted images[19,20]. Both thin-slice T2-weighted images and heavily-T2 weighted thick-slab images are acquired, the latter representing cholangiopancreatography images (MRCP) *per se*[21].

PRE-SURGICAL IMAGING CHARACTERIZATION OF INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS

The preoperative characterization of IPMN is challenging and frequently requires a multidisciplinary approach. Understanding the histopathological features of this disease is necessary for the correct interpretation of cross-sectional imaging studies[7,14,22-24]. IPMNs represent a spectrum of neoplasms composed of mucinous cells lining the main pancreatic duct and/or side branches. These tumors are characterized by the mucinous transformation of the pancreatic ductal epithelium which eventually leads to the development of the papillary projections typically seen at histological analysis[25]. Excessive mucin production by the neoplastic cells results in cystic dilatation of the pancreatic duct and/or branch ducts. The spillage of mucin from the ampulla of Vater causing a "fish-mouthed" ampulla is a classic, albeit uncommon, finding at endoscopic retrograde cholangiopancreatography (ERCP).

Although the natural history of the disease is not fully understood, a stepwise progression from benign adenomas to low- and high-grade dysplasia, in-situ-carcinoma, and then invasive carcinoma has been proposed[26,27]. IPMNs are also sub-classified as main pancreatic duct (MPD) (both segmental and diffuse), branch duct and mixed-type based on their site of origin and extent of tumor. Most branch duct lesions are benign whereas tumors involving the main duct are frequently associated with malignancy[26].

Cross-sectional imaging findings

A branch duct IPMN appears as a cluster of small cysts with lobulated margins that may be septated or as a single, unilocular cystic lesion at CT, US or MRCP. Branch duct IPMN is frequently located in the uncinate process of the pancreas although they can be found throughout the entire gland, particularly in the tail[23]. A characteristic communication between the branch duct IPMN and a normal-sized MPD can be seen on MRCP (Figure 1) and CT[11,28]. However, the MPD may also be dilated due to mucin secretion. With chronic obstruction of the MPD, pancreatic atrophy may also be present. Complex features in a branch duct IPMN include a thick, enhancing wall and septae, and nodules.

The main duct variant of IPMN can have either segmental or diffuse involvement of the duct. A segmental main duct IPMN may present as a cystic lesion that mimics the appearance of a mucinous neoplasm (i.e. cystadenoma, cystadenocarcinoma)[23]. The MPD in patients with 'cystic' segmental involvement, however, is frequently dilated because of the secretion of mucin by the tumor whereas the MPD in patients with mucinous neoplasms is typically normal[23].

Commonly, the entire MPD is diffusely dilated because profuse mucin impedes the flow of juice through the pancreatic duct. This phenomenon results in mod-

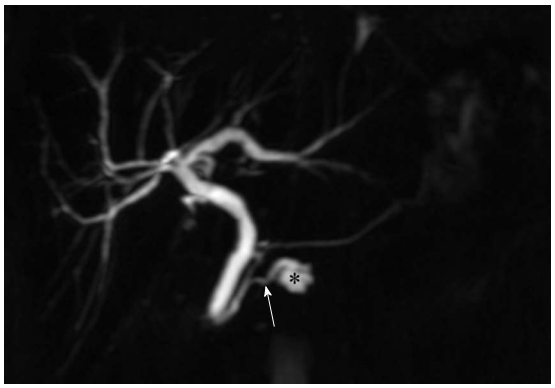

Figure 1 Coronal maximum intensity projection from a 3D T-weighted MRCP acquisition. A cystic lesion in the uncinate process of the pancreas (asterisk) and a communicating branch duct (arrow) between the cyst and the normal caliber main pancreatic duct. These findings are characteristic of a branch duct intraductal papillary mucinous neoplasms and this lesion has been stable on follow up MRCP examinations for 3 years.

erate-to-marked dilation of the entire MPD on cross-sectional imaging. Diffuse dilation of the MPD in IPMN is frequently associated with parenchymal atrophy and may be impossible to distinguish from chronic pancreatitis on imaging[23,28]. Similar to ERCP, a prominent papilla may also be present on CT and MRCP.

Diffuse wall thickening and enhancement of the MPD is a characteristic of advanced (i.e. malignant) main duct IPMN. Similarly, papillary excrescences or nodules of tumor may be seen arising from the walls of the dilated ducts, although they are often inconspicuous because of their small size and flat configuration. When visible, these nodules are hyperechoic on US, hyperattenuating at contrast-enhanced CT and hypointense on T2-weighted images[23]. Differentiation of mural tumor nodules and mucin globs can be challenging. A non-dependent location of these nodules along the wall of a dilated duct and the unequivocal demonstration of enhancement adds confidence about the presence of mural tumor excrescences (Figure 2). Mucin globs are mobile, do not enhance and are usually dependently located. Further imaging of the patient in different positions (i.e. supine and prone) can be helpful in demonstrating the mobility of mucin globs[23].

Mixed-type tumors demonstrate a combination of imaging features of branch-duct and main duct IPMN. Differentiation between branch duct and mixed type IPMN can be challenging. The MPD can be dilated both in patients with exclusive involvement of a branch duct by IPMN due to excessive mucin production by the cyst and in patients with mixed type IPMN. Therefore, the differentiation between branch-type and mixed-type IPMN may be virtually impossible. In these cases, the MPD must be carefully scrutinized for the presence of any wall thickening, enhancement or mural nodules that would indicate the presence of neoplastic involvement of the MPD.

Imaging predictors of malignancy and resectability in intraductal papillary mucinous neoplasms

The presence of malignant components in an IPMN has

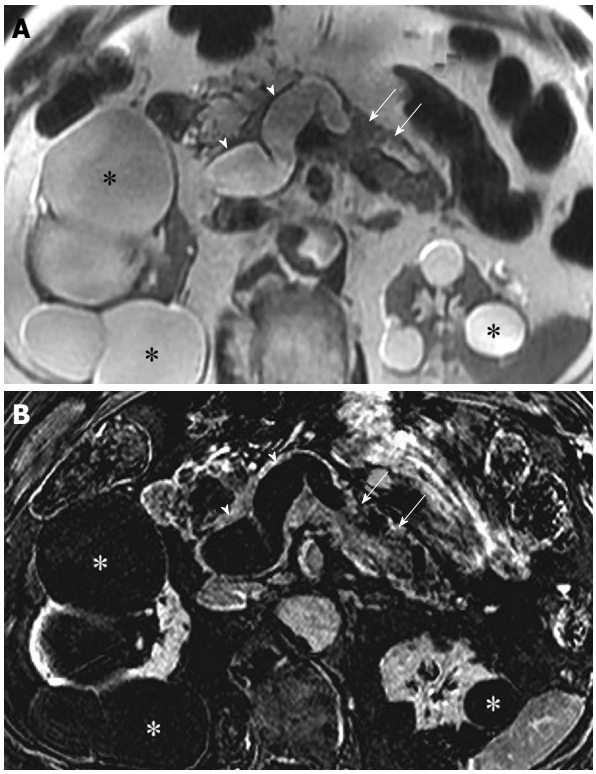

Figure 2 Axial T2-weighted (A) and subtraction (post-contrast minus pre-contrast) (B) images at the level of the pancreas. Marked enlargement of the main pancreatic duct (arrowheads) with intraluminal enhancing papillary projections (arrows). Main duct intraductal papillary mucinous neoplasms with *in situ* carcinoma was confirmed at histopathology after total pancreatectomy.

direct implications on the management of these lesions[15]. Imaging features that are indicative of malignancy in a branch and mixed type IPMN include the presence of solid nodules, thick enhancing walls and/or septae, a wide (> 1 cm) connection of a side-branch lesion with the MPD and the size of the tumor[10,16,29]. Specifically, a branch duct type IPMN greater than 3 cm in surgical specimens or preoperative imaging studies including transabdominal US, CT, endoscopic US, ERCP and MRCP has been correlated with malignancy, including carcinoma in situ and invasive carcinoma[30,31]. Others have found a cyst size > 40 mm as predictor of malignancy[10]. However, the absence of complex features (e.g. septae, nodules, thick wall) and enhancement, particularly on a high-quality MRCP, in an incidental asymptomatic branch duct IPMN likely indicates the absence of malignancy, even for IPMN > 3 cm in size.

The presence of a MPD > 6 mm, a mural nodule > 3 mm and an abnormal attenuating area in the adjacent pancreatic parenchyma on CT (Figure 3) correlates with malignant disease (i.e. *in situ* and invasive carcinoma) in IPMN[32]. The reported sensitivity, specificity, positive and negative predictive values and accuracy of these findings (with 2 or more present) for correctly characterizing these tumors as malignant are 83%, 81%, 85%, 78% and 82% respectively[32].

MRI depicts mural nodules in up to 60% of patients with malignant IPMN and 4% of patients with a benign or

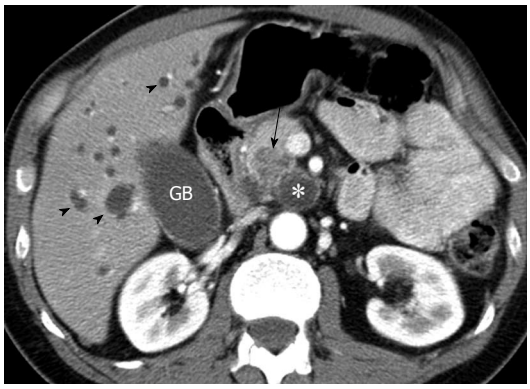

Figure 3 Axial contrast enhanced computed tomography image at the level of the head of the pancreas. A cystic lesion (asterisk) in the uncinate process of the pancreas with an hypoattenuating area (arrow) in the adjacent pancreatic parenchyma. Note intrahepatic biliary obstruction (arrowheads) due to obstruction of the common bile duct (not shown) by the infiltrating mass. Invasive pancreatic adenocarcinoma arising from an intraductal papillary mucinous neoplasms was confirmed at pathology after a Whipple procedure. GB: Gallbladder.

borderline IPMN[9]. Wall enhancement in the MPD after gadolinium administration is also more common in malignant (74%) than benign tumors (21%)[9]. Malignant tumors have a larger median diameter of the MPD (18 mm) than benign lesions (11 mm) on MRCP[9].

When analyzing the CT features of malignancy in IPMN, most lesions (93%) with mural nodules correlate with in situ carcinoma at histopathology whereas the majority (90%) of infiltrating masses represent IPMN with invasive carcinoma[13]. The size of the MPD and branch duct on CT does not seem to correlate with the presence of invasive disease[13]. The reported sensitivity and specificity of CT for detecting invasive disease are 81% and 96% respectively[10].

The overall accuracy of CT for predicting surgical resectability is 74%[13]. Using the standard CT criteria for adenocarcinoma, Viullerme *et al*[13] reported a positive predictive value of 100% for determining resectable disease in patients with IPMN. However, the same authors reported a poor positive predictive value (17%) for the CT characterization of unresectable disease. This was likely due to the common peripancreatic inflammatory changes that occur in these patients secondary to pancreatitis which results in peripancreatic fat stranding mimicking carcinomatosis on CT[13].

Magnetic resonance imaging vs computed tomography for characterization of intraductal papillary mucinous neoplasms

MRCP is superior to MDCT for demonstrating the communication between the MPD and a branch duct, allowing for a higher specificity in the diagnosis of IPMN with MRCP[14,33]. This communication is visible on MRCP and CT in 73% and 18% respectively of patients with branch and mixed type IPMN[14]. However, recent developments in multidetector CT technology provide superb, ultrafast isotropic resolution of the pancreas which allows for multiplanar and curved reformations for demonstration of communication between the branch duct cyst and the MPD with a reported sensitivity almost equivalent to that of MRCP[17].

MRCP also has a higher sensitivity than that of CT for detecting branch duct cysts due to the superior soft tissue contrast of MRI[14]. The potential implications of a more accurate definition of disease extent when using MRCP in patients with IPMN for proper cancer risk stratification and treatment decision making have been recently highlighted[14]. In addition, CT may overestimate the involvement of the MPD compared to MRCP using pathology as the standard of reference which could erroneously indicate the need for surgery[14].

Multidetector CT examinations provide superior sensitivity and specificity than that of single-slice CT examinations for the detection of invasive cancer in patients with IPMN[10]. However, it is important to emphasize that the malignant component of IPMN may not be detected by CT in up to 26% of malignant lesions[13]. While the majority of these missed lesions represent < 1 mm foci of in situ carcinoma, large invasive tumors may go undetected on CT examinations[13].

The authors' experience parallels the aforementioned differences between MRCP and CT, with the former being their imaging technique of choice for characterizing cystic disease in the pancreas. However, the authors prefer the use of CT angiography (CTA) for pre-surgical staging of pancreatic adenocarcinoma because of the exquisite demonstration of the relationship between the tumor and peripancreatic blood vessels as well as anatomic variants in the arterial vasculature. Similarly, a dedicated CTA of the pancreas may be justified prior to surgery for those patients with IPMN in whom an invasive carcinoma is suspected. Not infrequently, more than one imaging examination (i.e. CT, MRCP and endoscopic US) is necessary for selecting the best treatment option because of the challenges involved in characterizing cystic lesions of the pancreas.

FOLLOW-UP IMAGING STRATEGIES IN INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS

Imaging follow-up of presumed intraductal papillary mucinous neoplasms

The known malignant potential of IPMN and the increased detection of incidental asymptomatic pancreatic cysts due to the widespread use of cross-sectional imaging have resulted in an exponential increase of follow-up imaging performed for these lesions. The patient anxiety, radiation exposure and increase cost associated to repeated imaging may not be justified in all cases and follow-up strategies must be implemented.

An international consensus statement for management of IPMN and mucinous neoplasm of the pancreas recommended follow-up with annual CT or MRI for small (< 1 cm), asymptomatic, simple cysts[15]. In a recent study in patients without known or suspected pancreatic disease

Table 1 Follow up of incidental asymptomatic pancreatic cysts

Size (cm)	Age (yr)	Initial F/U	Subsequent F/U
< 1	< 70	1 yr	2 yr × 2, then every 3 yr
	> 70	No	No
1 - < 2	< 70	6 mo	6 mo × 1, 1 yr × 2, then every 2 yr
	> 70	6 mo	1 yr × 2, then every 2 yr
⩾ 2	Any	6 mo	6 mo × 2, 1 yr × 2, then every 2 yr

F/U: Follow up.

undergoing abdominal MRI at our institution, we found an overall prevalence of asymptomatic pancreatic cysts of 14%[2]. The prevalence increased with age and patients older than 70 years had a cumulative prevalence of 40%[2]. The mean diameter of the cysts was 7 ± 3.5 mm. These data support the idea that, much like renal cysts, incidental pancreatic cysts may be an acquired condition. Therefore, follow-up imaging of asymptomatic, simple (i.e. unilocular without internal architecture), small (< 1 cm) cysts may not be indicated. This approach should be particularly contemplated in older patients with other co-morbidities.

Larger cysts and those with internal architecture, particularly in younger patients, require active surveillance with imaging. Multiphasic CT examinations of the pancreas should be avoided because of the cumulative radiation dose of repeated examinations. Trans-abdominal US should be used for thin patients in whom this approach allows for appropriate evaluation of the cyst[15]. MRCP is the best alternative for following up these lesions when trans-abdominal US is not adequate. The need for gadolinium administration in follow-up MRI examinations has been questioned because of the ability of standard T2-weighted and MRCP images to demonstrate changes in size and internal architecture[34].

The interval between follow-up examinations and the length of the follow-up period remains to be determined. The international consensus recommendations for imaging annually cysts < 10 mm, every 6-12 mo cysts 10-20 mm and every 3-6 mo cysts > 20 mm, for 2 years[15] may now seem excessive. Given the overall prevalence of pancreatic cysts in asymptomatic patients and the substantial increase in number of cysts in the elderly population[2], new algorithms that take the patient's age into consideration are necessary.

The authors have recently implemented new guidelines for following up asymptomatic incidental pancreatic cysts at their institution (Table 1). With a better understanding of the natural history of these cysts, these recommendations may be modified in the future to decrease even further the number and frequency of imaging studies. For example, current recommendations for incidental pulmonary nodules detected on CT support avoiding further imaging of lesions < 4 mm in size for patients without risk factors[35]. Similarly, the authors anticipate using a size cut off to safely avoid the need of additional imaging for incidental pancreatic cysts. Further research is, however, needed to elucidate the need for follow up of very small pancreatic cysts.

To our knowledge, the duration of the imaging follow-up of pancreatic cysts has not been defined. Dismissal of a lesion after a defined period of confirmed stability would seem reasonable. Unfortunately, up to 11% of simple cysts undergoing active surveillance may grow and up to 5% may develop mural nodules on imaging; these correlate to adenoma and in situ carcinoma at pathology[5]. The mean time for developing mural nodules is 8.75 years after the initial diagnosis[5]. Furthermore, the development of invasive carcinoma in branch duct IPMN may occur 3-5 years after the initial diagnosis[36]. However, the slow progression that is characteristic of these tumors may allow for spacing of the follow-up interval if no changes have occurred over several years.

Imaging follow-up of surgically resected intraductal papillary mucinous neoplasms

For patients undergoing surgical resection, an imaging follow-up strategy should be based on the ultimate pathological diagnosis given the differences in the rates of tumor recurrence between invasive carcinoma (up to 90% within 3 years of partial or total pancreatectomy) and patients with in situ carcinoma, and borderline and benign disease (0% and 8% within 3 years after total or partial pancreatectomy respectively)[37].

Disease recurrence in the pancreas after resection of an IPMN may occur in at least 7% in non-invasive IPMN[15]. However, the benefit of follow-up imaging after resection of a non-invasive IPMN in an otherwise asymptomatic patient remains to be determined[15]. It is also unclear if the frequency of pancreatic recurrence is related to positive margins at the time of resection although this does not seem to have an effect on the mid-term survival or tumor recurrence[38].

Up to 40% of patients with a surgically resected IPMN with invasive carcinoma will relapse within 12 mo and their reported 5-year survival is 36%[39]. The most common anatomic locations for relapse include the remaining pancreas, lymph nodes and distant metastases[39]. Therefore, an abdominal CT or MRI at 3, 6 and 12 mo after surgery seems appropriate. After the first year, patients may be followed up every 6 mo[15].

CONCLUSION

The characterization of intraductal papillary mucinous neoplasms (IPMN) of the pancreas on imaging studies requires an understanding of the histopathological features of this disease. Imaging findings on computed tomography and magnetic resonance imaging correlate tightly with the presence of malignant degeneration in these neoplasms. Even though the majority of incidental pancreatic cysts represent benign entities, many of these represent IPMN or other malignant etiologies such as a mucinous neoplasm and therefore an appropriate follow-up regimen is imperative. As of yet, there is no consensus as to the definitive management strategy for patients with a suspected IPMN. Follow-up strategies for patients with

surgically resected IPMN must be tailored based on the presence or absence of invasive disease at pathology.

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TOPIC HIGHLIGHT

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Differentiating intraductal papillary mucinous neoplasms from other pancreatic cystic lesions

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Abstract

Intraductal papillary mucinous neoplasms (IPMN) can be difficult to distinguish from other cystic lesions of the pancreas. To understand better and discuss the current knowledge on this topic, the literature and the institutional experience at a large pancreatic disease center have been reviewed. A combination of preoperative demographic, historical, radiographic, laboratory data, as well as postoperative pathologic analyses can often distinguish IPMN from other lesions in the differential diagnosis.

Key words: Intraductal papillary mucinous neoplasms; Pancreatic cyst; Differential diagnosis; Pancreas cancer

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INTRODUCTION

Intraductal papillary mucinous neoplasm (IPMN) is defined as an intraductal grossly visible (typically ≥ 1.0 cm) epithelial neoplasm of mucin-producing cells, arising in the main pancreatic duct or its branches[1,2]. This relatively new term, IPMN, has replaced such terms as "mucin-producing tumor" and "mucinous ductal ectasia." Distinguishing IPMN from other cystic lesions of the pancreas can often be accomplished on clinical, endoscopic, cytological and radiographic grounds. The diagnostic entities that must be considered in patients with cystic lesions of the pancreas are IPMN, mucinous cystic neoplasm, serous cystadenoma, pancreatic pseudocyst, solid-pseudopapillary neoplasm, lymphoepithelial cyst, cystic neuroendocrine tumor, cystic degeneration of invasive pancreatic carcinoma, and other rare entities such as acinar cell cystadenocarcinoma. Here we briefly review the highlights in the literature, and then present our approach to differentiating IPMN from of other cystic lesions of the pancreas.

LITERATURE REVIEW

The literature prior to the 1996 World Health Organization (WHO) definition of IPMN is difficult to interpret owing to lack of consensus definition and inconsistent recognition of these lesions. The rising incidence of IPMNs since the 1990s may therefore be attributed to increased recognition and detection. Major advances in the literature since the 1996 WHO definition have included the publication of several large series, the Sendai guidelines, and nomograms to aid clinical decision-making (vide infra).

One of the largest single-institution series of IMPNs in the literature, from Johns Hopkins Hospital, was recently updated to include a total of 136 resections for IPMN[3,4]. These patients had a mean age of 67 years, and underwent either pancreaticoduodenectomy (71%), total pancreatectomy (15%), distal pancreatectomy (12%), or central pancreatectomy (2%). Patients were stratified into those who had an IPMN associated with an invasive carcinoma (38%) and those who had an IPMN without an associated invasive carcinoma (62%). Based on histological features, noninvasive lesions were categorized as having low-grade dysplasia (17%), moderate dysplasia (28%), or high-grade dysplasia (55%). Interestingly, those patients with an IPMN and an invasive carcinoma were older than those with a noninvasive IPMN with low-grade dysplasia (63 years *vs* 68 years; $P = 0.08$), with high-grade dysplasia patients having an intermediate age of 67 years, suggesting the possibility of a progression over years, akin to that observed in the progression from colon adenomas to invasive colon carcinomas. The overall 5-year survival of patients with noninvasive IPMNs was 77% while only 43% of patients with an IPMN with an associated invasive carcinoma survived 5 years. Other series[5-9] have found similar results regarding the demographics, the proportion associated with an invasive carcinoma, and 5-year survival. The largest collaborative series, from Massachusetts General Hospital and the University of Verona[5], was also recently updated. When branch-duct IPMN was compared to either main-duct or combined IPMN, there were significantly more low-grade dysplasias in the branch-duct group and significantly more IPMNs with an associated invasive carcinoma in the main-duct/combined group, an observation that is part of the foundation for the now widely recognized importance of recommending resection to patients with main-duct lesions, as expressed in consensus statements[10,11]. IPMNs that do progress to invasive cancer, however, have a significantly longer 5-year survival (42%) than do invasive ductal adenocarcinoma *not* associated with IPMN (19%; $P < 0.001$)[12].

The first adequate - and currently the most commonly employed - set of consensus guidelines regarding the clinical management of IPMNs was the Sendai International Consensus Guidelines, first published online in 2005 by the International Association of Pancreatology[10,11]. These guidelines addressed not only to the accurate diagnosis of IPMNs (*viz.* differentiating IPMN from mucinous cystic neoplasm), but the determination of which lesions warrant resection and which can be safely observed. Although the best choice of diagnostic imaging modality is largely institution-dependent, Tanaka *et al*[10,11] recommend magnetic resonance imaging (MRI) as the best modality to outline the gross appearance of the lesion and endoscopic retrograde cholangiopancreatography (ERCP) as the best method to identify ductal communication. The Sendai guidelines identify the presence of symptoms, a main-duct component, diameter > 3 cm, and any solid component as relative indications for resection in appropriately selected patients. We would add to this list rapid rate of growth and young age.

One very recent study has evaluated the use of Markov modeling and nomograms to assist with clinical decision-making in patients with small asymptomatic branch-duct IPMNs who are balancing the risks and benefits of resection versus observation: Weinberg *et al*[13] found that the decision to resect or observe depended on patient age and comorbidities, cyst size, and patients' valuing of overall survival versus quality-adjusted survival. For those valuing overall survival primarily, irrespective of quality of life, resection was optimal for lesions > 2 cm. Patients focused on quality of life however, required a 3-cm threshold for resection except for the extreme elderly.

DIFFERENTIATING INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM FROM OTHER LESIONS

Our approach for differentiating IPMN from other lesions is based on the distinguishing characteristics of these tumors and is presented in Tables 1 and 2. These characteristics have been identified from our experience at the Johns Hopkins Hospital and from the expanding body of literature on pancreatic cystic lesions.

When presented with a patient harboring a cystic lesion of unknown identity in the pancreas, one can often eliminate immediately several entities from the list of likely diagnoses, depending on the patient's demographics and history. For example, a helpful starting point is simply the question, What is the patient's gender? If the patient is male, then at least one diagnosis, mucinous cystic neoplasm, is very unlikely, as 95% of mucinous cystic neoplasms occur in women (Figure 1). Similarly if the patient does not have a history of pancreatitis then a diagnosis of pancreatic pseudocyst is virtually excluded (Figure 2). We then consider the patient's age, which is helpful if the patient is very young, since one of the diagnoses in the differential - solid-pseudopapillary neoplasm - tends to occur in young (and female) patients(Figure 3). Next we evaluate the patient's family medical history. Although uncommon, some patients with cystic lesions of the pancreas have a familial or personal history of von Hippel-Lindau (VHL) disease or multiple endocrine neoplasia (MEN), and VHL and MEN are associated with serous cystadenoma (Figure 4) and cystic neuroendocrine neoplasms (Figure 5), respectively.

The next most available information after demographics and history is typically imaging data. The baseline imaging modality of choice is largely institution-dependent. Some centers rely heavily on endoscopic ultrasound (EUS) or magnetic resonance imaging (MRI). At our institution, computed tomography (CT) imaging of the pancreas and its interpretation are exceptionally good, so we tend to use it very often, especially as an initial screening tool. We also use EUS to look for nodules and to obtain tissue or fluid when indicated. MRI, especially in combination secretin stimulation, is used selectively and can be quite sensitive in following smaller cysts in the pancreas. As with male gender, location of the cyst in the head of the pancreas significantly reduces the likelihood that the lesion is a mucinous

Table 1 Distinguishing features of pancreatic cystic lesions[1,14-19]

Typical characteristics	IPMN	MCN	SC	PSEUDO	SPN	LEC	cNET	cPDAC
Age Group	Elderly	Middle	Middle-Elderly	Any	Young	Elderly	Middle-Elderly	Elderly
Gender	70% male	95% female	> 50% female	> 50% male	80%-90% female	80% male	50% each	> 50% male
History	Asx; Pain; ± jaundice	Asx; Pain; nausea	Asx; VHL	Pancreatitis	Asx; Pain; nausea	Asx	Asx; Fxnl; MEN	Asx; Pain; ± jaundice
Location in pancreas	Head in 70%; Multi-focal	Body/Tail in 95%	Anywhere	Anywhere	Anywhere	Peripheral	Anywhere	Anywhere
Shape	Ovoid	Spheroid	Ovoid	Spheroid	Ovoid	Ovoid	Spheroid	Variable
Locularity	Any	Uni or Oligo	Oligo or Multi	Uni	Oligo or Multi	Oligo	Uni	Any
Duct Com-munication	Common	No	No	Common	No	No	No	Some
Calcification	No	No	Central sunburst	No	Some	No	Some	No
Cyst fluid appearance	Viscous, clear, muc	Viscous, clear, muc	Thin, clear, nonmuc	Opaque, bloody/ necrotic debris	Opaque, bloody/ necrotic debris	Nonmuc, crystalline debris	Nonmuc	Thin
High CEA/Mucin[a]	+	+	-	-	-	-	-	±
High Ca 19-9	±	±	-	-	-	-	-	±
High amylase	+	-	-	+	-	-	-	±
Epithelium	Columnar, Papillary	Columnar	Cuboidal	No epithelium	Poorly cohesive cells with nuclear grooves	Squamoid	Uniform	Gland-forming
Stroma	Fibrotic	Ovarian	Fibrotic	Fibrotic	Sometimes hyalinized	Lymphoid	Sometimes hyalinized	Fibrotic

[a]May be positive in cases of luminal contamination of endoscopic needle aspirate. IPMN: Intraductal papillary mucinous neoplasm; MCN: Mucinous cystic neoplasm; SC: Serous cystadenoma; PSEUDO: Pancreatic pseudocyst; SPN: Solid-pseudopapillary neoplasm; LE: Lymphoepithelial cyst; cNET: Cystic neuroendocrine tumor; cPDAC: Pancreatic ductal adenocarcinoma with cystic degeneration; VHL: Von hippel-lindau disease; Muc: Mucinous; Nonmuc: Nonmucinous; Asx: Asymptomatic; Fxnl: Functional. These data are derived generalizations of the literature, with the understanding that there is significant overlap among cyst types and there are inherent sampling errors associated with various tests; diagnostic and treatment decisions should not rely solely on the information presented in this review. An electronic worksheet version of this table is available at http://pathology.jhu.edu/pancreas/professionals/ipmn.php

Table 2 Key questions to aid in making likely diagnoses[19]

	Key question	Likely diagnoses to consider
Demographics and history	Male?	MCN unlikely
	No history of pancreatitis?	PSEUDO unlikely
	Young female?	SPN
	History of MEN?	cNET
	History VHL?	SC
Imaging	Spheroid?	PSEUDO or MCN
	Central sunburst calcification?	SC
	Location in head?	MCN unlikely
Cyst fluid	No CEA/mucin?	IPMN or MCN unlikely
	High CEA, high amylase?	IPMN
	High CEA, low amylase	MCN
	Low CEA, high amylase?	PSUEDO
	High amylase?	IPMN or PSEUDO
Histology	Epithelial lining?	PSEUDO unlikely
	Ovarian stroma?	MCN

IPMN: Intraductal papillary mucinous neoplasm; MCN: Mucinous cystic neoplasm; SC: Serous cystadenoma; PSEUDO: Pancreatic pseudocyst; SPN: Solid-pseudopapillary neoplasm; VHL: Von hippel-lindau disease; MEN: Multiple endocrine neoplasia. These data are derived generalizations of the literature, with the understanding that there is significant overlap among cyst types and there are inherent sampling errors associated with various tests; diagnostic and treatment decisions should not rely solely on the information presented in this review. An electronic worksheet version of this table is available at http://pathology.jhu.edu/pancreas/professionals/ipmn.php

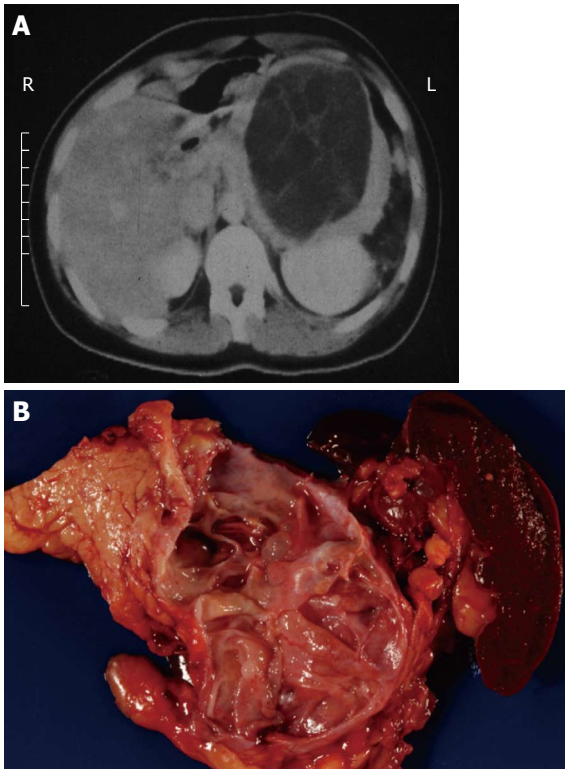

Figure 1 Typical computed tomography (A) and gross (B) appearance of a mucinous cystic neoplasm showing the distal location and the lack of communication with the duct, respectively.

cystic neoplasm, as most mucinous cystic neoplasms arise in the body or tail of the gland. Simply assessing the shape of the lesion may also help, as many mucinous cystic neoplasms and serous cystadenomas are often spherical. Using ERCP, MRCP, or (as discussed below) determination of the amylase content of fluid obtained by fine needle aspiration, one may next answer the key question, Does

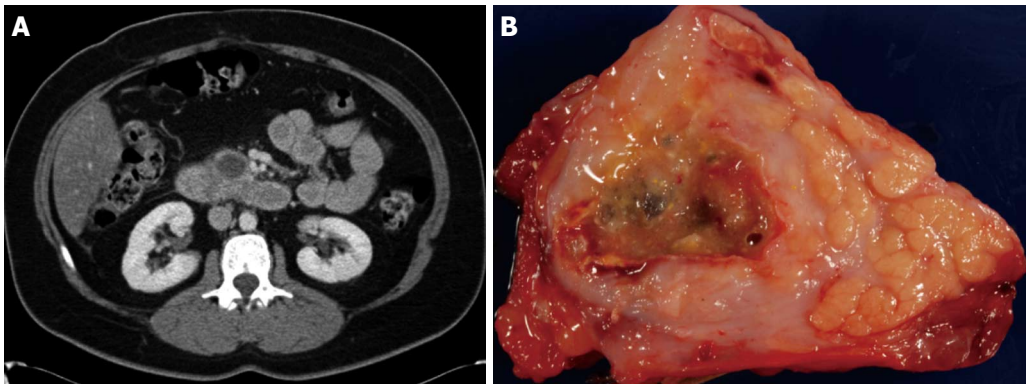

Figure 2 Typical computed tomography (A) and gross (B) appearance of a small pancreatic pseudocyst showing the typical spheroid shape, unilocularity, and necrotic debris contents.

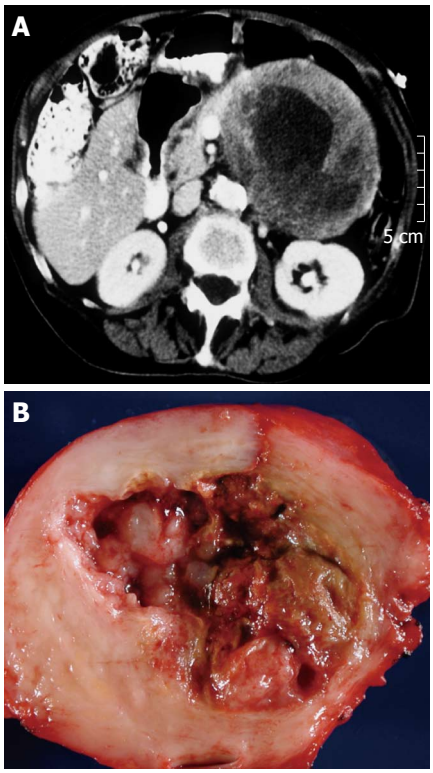

Figure 3 Typical computed tomography (A) and gross (B) appearance of a solid pseudopapillary neoplasm showing the typical ovoid shape and necrotic debris contents.

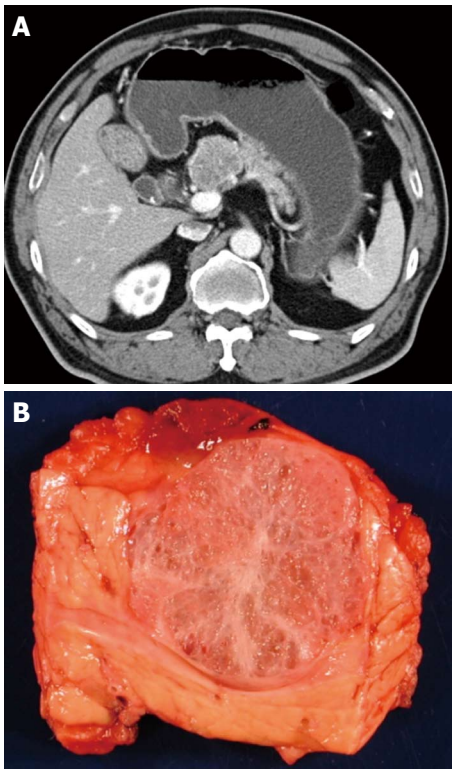

Figure 4 Typical computed tomography (A) and gross (B) appearance of a serous cystadenoma showing the honeycomb appearance.

the cyst communicate with the pancreatic duct (Figure 1)? We have found ERCP and fluid amylase concentration to be more sensitive and more reliable than MRCP. An affirmative answer here, in the absence of a history of pancreatitis, weighs heavily in favor of a diagnosis of IPMN since the vast majority of the other cystic lesions do not communicate with the duct system (Figure 6). Finally, the identification of a typical sunburst pattern of central calcification or honeycomb appearance is virtually pathognomonic for serous cystadenoma (Figure 4).

The character of the cyst fluid, which is often ascertained at the time of EUS and fine needle biopsy, can also help in the differential diagnosis. The first and easiest characteristic to assess is the gross appearance of the cystic fluid: viscous, mucinous fluid is consistent with IPMN or mucinous cystic neoplasm, while opaque fluid with necrotic or hemorrhagic debris is typical of pancreatic pseudocyst or solid-pseudopapillary neoplasm, and fluid that is thin (nonmucinous) and clear (may be straw-colored or blood-stained) is usually seen with serous cystadenoma and the less common lymphoepithelial cyst (Figure 7), cystic neuroendocrine neoplasm, and invasive carcinoma with cystic degeneration (Figure 8).

Laboratory evaluation of the cyst fluid can also help focus the differential diagnosis. Most commonly, positive mucin staining or high levels of CEA, while sometimes the result of gastrointestinal luminal contamination, supports a diagnosis of either IPMN or mucinous cystic neoplasm, which can be distinguished from each other by the cyst fluid amylase level (high in IPMNs communicat-

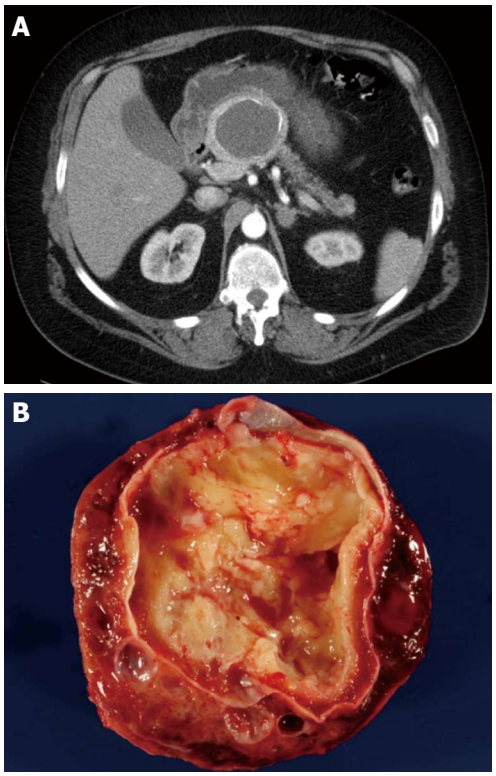

Figure 5 Typical computed tomography (A) and gross (B) appearance of a cystic neuroendocrine tumor showing the spherical shape and the occasionally seen calcification.

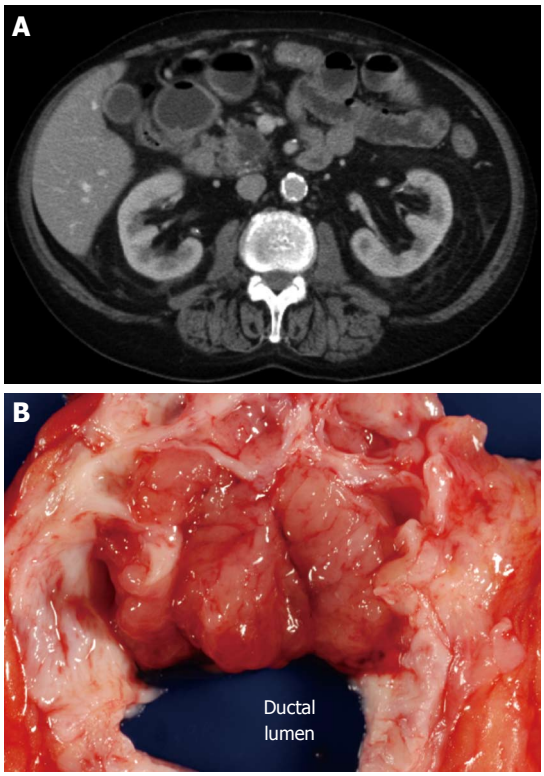

Figure 6 Typical computed tomography (A) and gross (B) appearance of an intraductal papillary mucinous neoplasm showing the ovoid shape and communication with the duct, respectively.

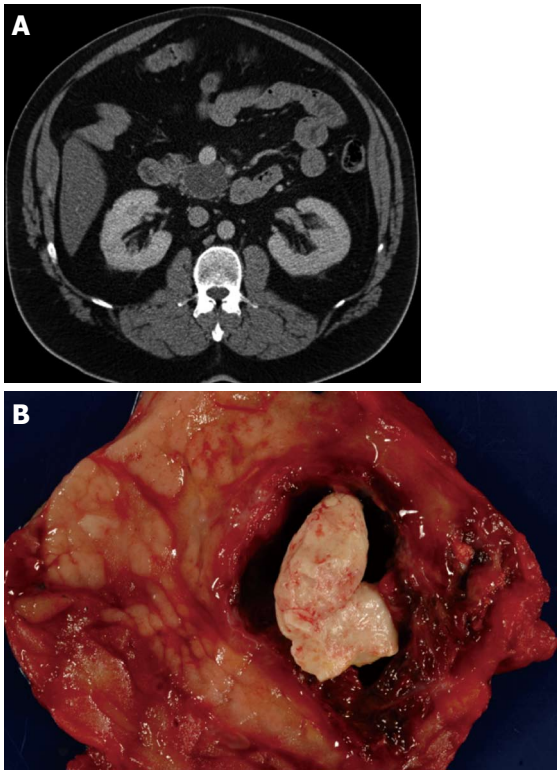

Figure 7 Typical computed tomography (A) and gross (B) appearance of a lymphoepithelial cyst showing the typical ovoid shape, peripheral location, and proteinaceous concretions (not always present on computed tomography imaging).

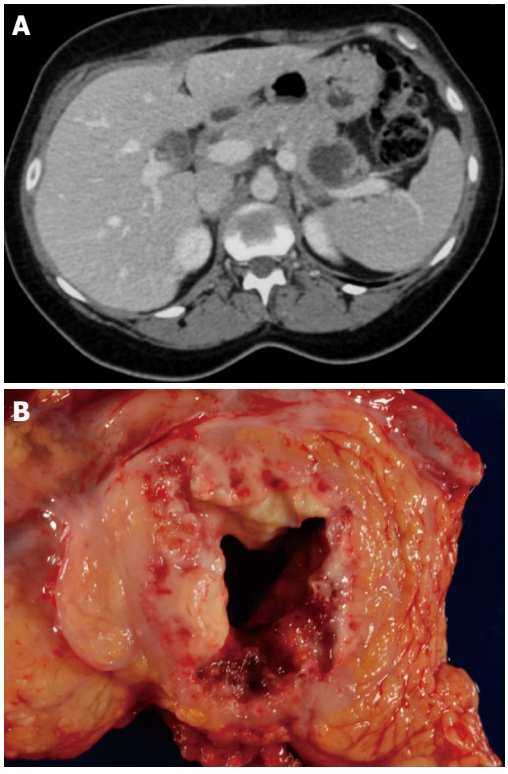

Figure 8 Typical computed tomography (A) and gross (B) appearance of an invasive carcinoma with cystic degeneration.

ing with the duct and low in mucinous cystic neoplasm, which do not communicate with the duct). The absence of mucin or low levels of CEA make IPMN and mucinous cystic neoplasm less likely diagnoses, pushing higher

on list of possible diagnoses serous cystadenoma, pancreatic pseudocyst, and solid-pseudopapillary neoplasm. While pancreatic pseudocyst can be eliminated if the cyst amylase levels are low, serous cystadenoma and solid-pseudopapillary neoplasm have similar cyst fluid laboratory profiles.

Of course the goal is to be able to make the diagnosis prior to resection, but diagnostic uncertainty can persist until the final pathologic examination of the resected specimen. Pseudocysts lack an epithelial lining, IPMNs are composed of columnar mucin-producing cells that involve the pancreatic duct system, mucinous cystic neoplasms have ovarian-type stroma, and solid-pseudopapillary neoplasms are composed of loosely cohesive cells and delicate branching blood vessels.

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TOPIC HIGHLIGHT

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Diagnostic and therapeutic endoscopic approaches to intraductal papillary mucinous neoplasm

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Abstract

Pancreatic cystic lesions are increasingly identified on routine imaging. One specific lesion, known as intraductal papillary mucinous neoplasm (IPMN), is a mucinous, pancreatic lesion characterized by papillary cells projecting from the pancreatic ductal epithelium. The finding of mucin extruding from the ampulla is essentially pathognomonic for diagnosing these lesions. IPMNs are of particular interest due to their malignant potential. Lesions range from benign, adenomatous growths to high-grade dysplasia and invasive cancer. These mucinous lesions therefore require immediate attention to determine the probability of malignancy and whether observation or resection is the best management choice. Unresected lesions need long-term surveillance monitoring for malignant transformation. The accurate diagnosis of these lesions is particularly challenging due to the substantial similarities in morphology of pancreatic cystic lesions and limitations in current imaging technologies. Endoscopic evaluation of these lesions provides additional imaging, molecular, and histologic data to aid in the identification of IPMN and to determine treatment course. The aim of this article is to focus on the diagnostic and therapeutic endoscopic approaches to IPMN.

INTRODUCTION

Pancreatic cystic lesions are increasingly identified with the widespread use of state-of-the-art imaging[1]. In particular, intraductal papillary mucinous neoplasms (IPMNs) have become a major clinical focus as a result of their increased identification and our modest understanding of their long term natural history. IPMNs are mucinous lesions that arise from the epithelial lining of the main pancreatic duct or its side branches and are characterized by neoplastic, mucin-secreting, papillary cells projecting from the pancreatic ductal surface[2]. IPMNs range from premalignant lesions with low-grade dysplasia to invasive malignancy. Clinically, patients may present with recurrent abdominal pain, nausea, or vomiting from pancreatitis, but IPMNs are most commonly asymptomatic and discovered incidentally on routine imaging. Diagnosis of IPMN with multi-detector computed tomography (MDCT) and magnetic resonance imaging (MRI) is frequently used, but still has limitations in distinguishing main duct from branch duct type IPMN (BDIPMN)[3] and in differentiating the broad spectrum of pancreatic cystic lesions[4-7]. Endoscopic evaluation of these lesions provides additional imaging, molecular, and histological data to aid in the identification

of IPMN and to determine treatment course. The aim of this article is to focus on the diagnostic and therapeutic endoscopic approaches to IPMN.

DIAGNOSTIC APPROACHES TO INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM

Endoscopic retrograde cholangiopancreatography

In the past, endoscopic retrograde cholangiopancreatography (ERCP) was used as the gold standard imaging tool for the diagnosis of IPMN. Characteristic findings at ERCP include a dilated main pancreatic duct with mucinous filling defects. Today, high resolution MDCT, MRCP, and endoscopic ultrasound imaging have replaced the routine use of ERCP alone. While ERCP can accurately assess ductal communication, there are cases where cystic side branches do not fill with contrast due to mucus plugging and an incorrect diagnosis is made. In some cases a bulging ampulla, sometimes referred to as 'fish-eye' ampulla, is seen extruding thick mucin and this is virtually pathognomonic of IPMN. Despite its diminishing role in the diagnosis of IPMN, ERCP maintains a principal advantage by permitting cytological sampling of suspected IPMN and facilitating evacuation of mucin from plugged pancreatic ducts. In addition, ERCP has many potential applications as a platform for endoscopic technologies under current development.

Endoscopic ultrasound

Endoscopic ultrasound (EUS) has been increasingly used to identify and characterize suspected IPMNs among other pancreatic cystic lesions. Aithal *et al*[8] demonstrated that EUS can be a useful tool in determining the presence of IPMN and that characteristic imaging features such as dilated pancreatic duct, cysts, and pancreatic atrophy were seen more commonly in patients with IPMN versus patients with chronic pancreatitis. EUS had a sensitivity and specificity of 86% and 99% respectively in the detection of IPMN. The ability of EUS to discriminate benign from malignant IPMNs has been shown to have a sensitivity of 75%-90% and a specificity of 71%-91%[9,10]. In order to better discriminate benign from malignant neoplasms, Sai *et al*[11] proposed pancreatic-duct-lavage cytology of BDIPMNs. Endoscopic retrograde pancreatography was performed to identify an area of ectatic side branches. A specially designed 5F double lumen cytology catheter was next introduced into the pancreatic duct over an existing guidewire and advanced to the dilated side branch. Saline solution was instilled in small volumes then aspirated and the fluid sent for cytological evaluation. The technique had a sensitivity of 78% and specificity of 93% and may provide a preoperative tool to help reduce unnecessary pancreatic surgery in patients with benign lesions that might otherwise meet current criteria for resection.

Endoscopic ultrasound guided fine needle aspiration to perform molecular analysis

The use of fine needle aspiration (FNA) to obtain cyst fluid aspirate facilitates the quantitative analysis of molecular markers such as carcinoembryonic antigen (CEA), which has been shown to be more accurate in the diagnosis of mucinous lesions than EUS and cytology[12]. Additionally, molecular analysis with the commercially available PathfinderTG can aid in preoperative diagnosis of malignant and benign mucinous pancreatic cysts[13]. A recent report of pancreatic cyst fluid DNA analysis, referred to as the PANDA study[14], demonstrated that DNA analysis diagnosed malignancy in all cases where cytology with FNA was negative. The most specific test for cystic malignancy was K-ras followed by allelic loss (96%). Additionally, K-ras mutations were associated with mucinous cystic lesions with a specificity of 96%, but sensitivity of only 45%. Pitman *et al*[15] reported that cyst fluid analysis in BDIPMNs less than 3 cm added enhanced diagnostic capabilities when the criteria of CEA > 2500 ng/mL or atypical epithelial components seen on cytology were found. In practice, it is likely that a combined approach to cyst fluid analysis will ultimately be the most diagnostic. The combination of CEA and molecular analysis has been shown to have a 100% sensitivity for diagnosing mucinous cysts; however, CEA level did not correlate well with the quantity of DNA[16].

Peroral pancreatoscopy

Pancreatoscopy involves the introduction of a small caliber endoscope, *via* a duodenoscope, into the pancreatic duct to directly observe the ductal epithelium. The characteristic findings of IPMN include a papillary tumor with 'fish-egg' like appearance, granular mucosa, or mucin[10]. Filling defects seen on ERCP suggestive of a pancreatic stone or main duct IPMN can be differentiated with peroral pancreatoscopy (POPS) and this permits biopsy of the pancreatic duct for histopathologic review. In one study, POPS alone was found to have a sensitivity of 100% in differentiating benign from malignant main duct IPMN, although the sensitivity was poor, 43% for BDIPMN[17]. Preoperatively, POPS can aid in surgical planning by delineating the extent of pancreatic ductal disease and identifying surgical margins (i.e. helping to regionalize a main duct IPMN) through direct visualization of the pancreatic duct epithelium and site-directed biopsy[10,18,19].

Intraductal ultrasound

Intraductal examination of the main pancreatic duct and surrounding structures using high frequency ultrasound probes has been demonstrated. Hara *et al*[17] showed that intraductal ultrasound (IDUS) alone has a better sensitivity and specificity for differentiating benign from malignant BDIPMNs (sensitivity 77% and specificity 100%) versus the main duct type (sensitivity 56% and specificity 71%). The combined use of POPS and IDUS resulted in the greatest accuracy (88%) for differentiating neoplastic

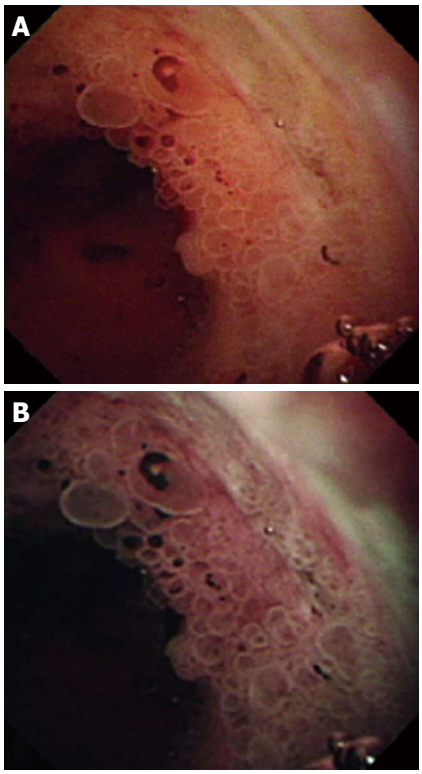

Figure 1 Peroral pancreatoscopy images. A: Peroral pancreatoscopy of the main pancreatic duct demonstrating the presence of papillary tumor; small, ovoid papillary projections can be seen; B: The same projections are pictures here under observation with narrow band imaging; the surface structure of the lesions is much better visualized. (The figure is from Itoi *et al*[20] and reproduced with permission from *Elsevier Inc*.)

lesions when compared to the use of CT, EUS, POPS, or IDUS alone. However, one group reported a respective sensitivity and specificity of 94% and 29% for the ability of IDUS to differentiate neoplastic from non-neoplastic lesions[10]. Taking into account size, Yasuda *et al*[19] showed that IDUS had a sensitivity of 100% for detecting protruding polypoid lesions higher than 3 mm in the pancreatic duct.

Narrow band imaging

The use of narrow band imaging (NBI) in examining ductal pancreatic lesions is limited. NBI functions by narrowing the spectral bandwidth of red-green-blue optical filters and thus emphasizes mucosal structures. NBI has been combined with POPS in a case series study of patients with IPMN and the results indicated improved visualization of the pancreatic duct surface structures and microvessels[20] (Figure 1). The improved visualization permits targeted sampling of extraordinarily small lesions. However, the technology is limited to patients with dilated pancreatic ducts and directed biopsies can be challenging given the tortuousness of the pancreatic duct.

Optical coherence tomography

Optical coherence tomography (OCT) is a probe-based imaging modality that provides micrometer resolution images of duct epithelium. Studies of solid lesions using

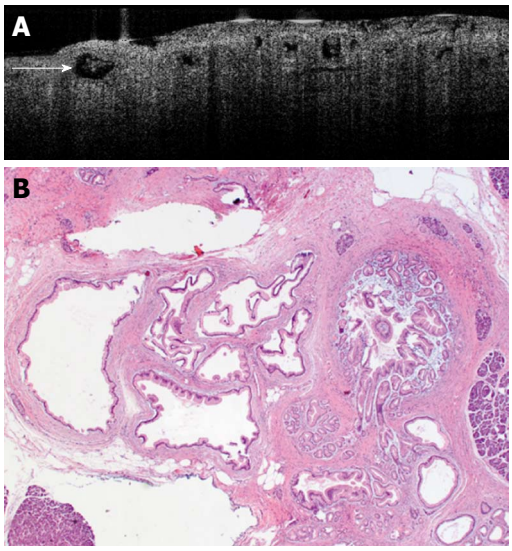

Figure 2 An optical coherence tomography image of a patient with borderline intraductal papillary mucinous neoplasm (A) and photomicrograph of an intraductal papillary mucinous adenoma in the same patient (B). A: Multiple cystic lesions are pictured here with medium to high scattering in the cyst cavity; the scattering suggests the existence of mucin. A single, mucinous cystic lesion is indicated by the white arrow and scattering is clearly seen within the cystic structure. Image provided courtesy of Dr. Sevde Cizginer at Massachusetts General Hospital, Boston, MA: B: Photomicrograph of an intraductal papillary mucinous adenoma in the same patient. The cysts are lined by a single layer of foveolar-type epithelial cells. Focally, papillary areas are identified. Image provided courtesy of Dr. Vikram Deshpande at Massachusetts General Hospital, Boston, MA.

pancreatic intraductal OCT demonstrated its feasibility and its superiority to brush cytology in distinguishing neoplastic from non-neoplastic lesions[21,22]. Until recently, application of this novel imaging modality to pancreatic cystic lesions had never been attempted. An *ex-vivo* OCT study of resected pancreatic tissue specimens containing cystic lesions, including IPMNs, demonstrated a 94% accuracy for differentiating serous cystadenomas from mucionous cystic neoplasms and IPMNs[23]. Application of this technology in a catheter-based system may provide high-resolution images of the pancreatic duct and immediately surrounding structures that can be obtained at ERCP or EUS-FNA examination (Figure 2).

ENDOSCOPIC TREATMENT OF INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM

Ethanol ablation

Generally, the resection of main and mixed variant IPMNs is recommended, although the long-term natural history of BDIPMNs in particular make the timing of surgical resection difficult. Furthermore, patients with significant morbidity are precluded from surgery and therefore definitive treatment. Less invasive therapies such as chemical ablation of pancreatic cysts offer an alternative. Initial studies of cyst ethanol ablation demonstrated the feasibility and safety of this approach and the potential promise of long term cyst resolution in some patients[24].

DeWitt *et al*[25] recently conducted a randomized, double-blind study of EUS-guided ethanol versus saline injection of pancreatic cysts. The study enrolled patients with cysts not communicating with the main duct. The participating subjects were heterogeneous and contained IPMNs, MCNs, and perhaps simple cysts among others. While the study was not specifically for IPMNs alone, the authors reported complete pancreatic cyst ablation in 33.3% of injected cysts on follow-up CT; there was a significant decrease in cyst surface area ($P = 0.009$) in all patients who received ethanol as opposed to saline lavage. Further studies focusing on cysts with imaging morphology characteristic of BDIPMN alone are needed. The EUS 2008 working group published a document that summarized potential roles for this ablative technique and provided recommendations for areas of future research[26].

Combination therapy and other alternatives

EUS-guided injection of ethanol/paclitaxel into the pancreas resulted in complete resolution of pancreatic cysts in 11 of 13 patients (84.6%) undergoing successful injection[27]. In 2 patients, partial cyst resolution was observed. The group reported acute pancreatitis in one patient. Future studies may include the testing of immunomodulatory drugs, radiopharmaceuticals, or other chemotherapeutic agents delivered in a variety of media.

CONCLUSION

The diagnosis of pancreatic IPMN and the decision of whether to resect or observe remains an ongoing challenge for the clinician. Significant imaging advances have helped to ensure more accurate diagnosis and better characterization of IPMNs which in turn helps guide long-term management. Current and evolving endoscopic techniques add exciting diagnostic tools to our imaging arsenal and provide a conduit for performing minimally invasive therapeutic treatments of IPMN.

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TOPIC HIGHLIGHT

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Differences between main-duct and branch-duct intraductal papillary mucinous neoplasms of the pancreas

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Abstract

In the last decade, intraductal papillary mucinous neoplasms (IPMNs) have become commonly diagnosed. From a morphological standpoint, they are classified in main-duct IPMNs (MD-IPMNs) and branch-duct IPMNs (BD-IPMNs), depending on the type of involvement of the pancreatic ductal system by the neoplasm. Despite the fact that our understanding of their natural history is still incomplete, recent data indicate that MD-IPMNs and BD-IPMNs show significant differences in terms of biological behaviour with MD-IPMNs at higher risk of malignant degeneration. In the present paper, clinical and epidemiological characteristics, rates of malignancy and the natural history of MD-IPMNs and BD-IPMNs are analyzed. The profile of IPMNs involving both the main pancreatic duct and its side branches (combined-IPMNs) are also discussed. Finally, general recommendations for management based on these differences are given.

Key words: Intraductal papillary mucinous neoplasms; Branch-duct; Main-duct; Malignancy; Surgery; Follow-up; Nodules; Combined type

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INTRODUCTION

In 1982, Ohhashi *et al*[1] from Japan described four cases of pancreatic cancer characterized by overproduction of mucus, diffuse dilatation of the pancreatic ductal system and presence of bulging papilla. In the next decade, small case reports from Europe and the United States referred to this condition as "mucinous ductal ectasia"[2-4]. Only in 1996 were these lesions defined as intraductal papillary mucinous neoplasms (IPMNs) by the World Health Organization (WHO) classification for tumors of the exocrine pancreas[5]. Main-duct IPMNs (MD-IPMNs) are characterized by involvement of the main pancreatic duct with or without associated involvement of the branch ducts (combined IPMNs); they usually present as a dilated ($\geqslant$ 1 cm) main pancreatic duct or as cystic dilation of the main duct and its branches; branch-duct IPMNs (BD-IPMNs) originate in the side branches of the pancreatic ductal system, appearing as a cystic lesion that always communicates with a non-dilated main pancreatic duct[6].

In the last ten years, the diagnosis of IPMNs has significantly increased[7,8]. This can be related to improved

imaging techniques, greater awareness of this condition by the gastroenterological community and incidental diagnosis among asymptomatic individuals.

The distinction among different IPMN sub-types is not only of "morphological" significance but has a practical impact on the management of patients with IPMNs. In this paper, we will review the clinico-pathological and epidemiological characteristics of IPMNs, their natural history and risk of malignancy with some guidelines for their management.

CLINICAL AND EPIDEMIOLOGICAL CHARACTERISTICS

IPMNs are typically found in elderly people. In most series, the median age of patients at the diagnosis is 65-70 years[6,8-19]. However, while a few studies made a clear distinction between MD-IPMNs and BD-IPMNs, most series include both subgroups. We recently have analyzed the clinical and epidemiological characteristics of a large series of IPMNs who underwent surgical resection at the University of Verona and at the Massachusetts General Hospital[20]. One hundred and fifty-nine patients had histologically confirmed BD-IPMNs while 81 had MD-IPMNs. Median age at presentation was similar in the two groups (66 and 67 years respectively) as well as a family history of pancreatic cancer (7.5% of MD-IPMNs and 11% of BD-IPMNs) and the presence of extra-pancreatic neoplasms (22% of MD-IPMNs and 20% of BD-IPMNs). The most common extra-pancreatic neoplasms were breast, colorectal, lung and prostate cancer. Other reports suggest that patients with IPMNs are at higher risk of developing extra-pancreatic tumors if compared with the general population and, in keeping with our data, colorectal cancer and adenomatous polyps are commonly found in IPMNs patients[21-24]. Interestingly, BD-IPMNs were most commonly found in females (57%) and MD-IPMNs in males (55.5%). BD-IPMNs and MD-IPMNs were found in the proximal pancreas in 64% and 52% of cases respectively and BD-IPMNs were more frequently associated with a diffuse pattern (23% *vs* 4%)[20].

Moreover, while BD-IPMNs are characterized by the presence of multifocal cystic lesions in different sites of the gland (sometimes with a complete involvement of the entire pancreas), MD-IPMNs spread along the main pancreatic duct, also possibly being skip lesions[25].

Clinically, BD-IPMNs were more frequently discovered in asymptomatic individuals (34.5% *vs* 13.5%). Abdominal pain was common in both MD-IPMNs and BD-IPMNs but in many cases it was an aspecific symptom. On the other hand, more specific and objective symptoms such as jaundice and weight loss were significantly associated with the presence of MD-IPMNs[20]. The main features of both IPMNs are briefly summarized in Table 1.

NATURAL HISTORY AND RISK OF MALIGNANCY

Our knowledge of the natural history of IPMNs is still incomplete but a better awareness of the distinction between the main and branch duct variants have contributed to a better understanding. It is well known that IPMNs can show a series of dysplastic changes from adenoma to invasive carcinoma and that different degrees of dysplasia can be found within the same lesion[5,6,26,27]. The frequency of malignancy (*in-situ* and invasive carcinoma) in MD-IPMNs is high, ranging between 60% and 92% with a mean of 70%[6,10,16-19]. The largest published series on MD-IPMNs combines the experience of Massachusetts General Hospital and University of Verona with 140 resected patients[18]. In this study, we found that patients with malignant MD-IPMNs were significantly older by 6.4 years than those with benign ones. The experiences from Johns Hopkins[10] and Indiana University[16] confirmed this observation, showing that patients with MD-IPMNs with invasive cancer are older than those with noninvasive neoplasms by 5 years. These findings suggest that most, if not all, MD-IPMNs can progress to malignancy.

By contrast, in BD-IPMNs the frequency of malignancy is significantly lower (between 6% and 46%, with a mean of 25%) and that of invasive cancer ranges from 0 to 30% (mean of 15%)[6,8,9,10-16]. In the combined experience of Massachusetts General Hospital and University of Verona, 145 patients underwent surgical resection for BD-IPMNs[9]. Of these, 32 (22%) had malignancy but there was invasive carcinoma in only 11% (16 patients) with no age difference between benign and malignant tumors (66 years *vs* 67.5 years). Schmidt *et al*[16] and Peleaz-Luna *et al*[13] reported a rate of malignancy of only 19% and 12% in their series of 103 and 77 patients who underwent surgery for BD-IPMNs. Levy *et al*[12] calculated the longitudinal risk of malignant transformation since the first clinical or radiological sign in a series of 106 patients with histologically proven IPMNs or probable IPMN (30 patients with a radiological diagnosis of BD-IPMNs). Overall ten year actuarial risk of occurrence of IPMNs with low-grade dysplasia, high-grade dysplasia and invasive cancer was 67%, 49% and 29% respectively. Five year actuarial risk of malignancy was 15% for BD-IPMNs and 63% for MD-IPMNs ($P < 0.001$).

THE PROFILE OF COMBINED-INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS

Combined-IPMNs are characterized by an involvement of both the main pancreatic duct and the branch-ducts of the pancreas by the tumor. Combined-IPMNs have historically been considered as an extension of MD-IPMNs into the side branches of the ductal system[6,18]. However, it is unclear if combined-IPMNs represent a progression of MD-IPMNs, a progression of multifocal BD-IPMNs or if they represent a disease itself with a specific profile. In this light, we have recently compared the clinical and epidemiological characteristics of 159 patients with BD-IPMNs, 81 MD-IPMNs and 149 combined-IPMNs in order to elucidate differences among the three groups[20].

Table 1 Epidemiological and clinicopathological characteristics of patients with main-duct, branch-duct and combined intraductal papillary mucinous neoplasms *n*,%

	Main duct IPMNs (*n* = 81)	Branch duct IPMNs (*n* = 159)	*P* value, MD *vs* BD
Median age, yr (range)	67 (37-85)	66 (35-90)	n.s.
Sex			
Female	36 (44.5)	91 (57)	0.04
Male	45 (55.5)	68 (43)	
Positive family history of pancreatic cancer	6 (7.5)	16 (11)	n.s.
Positive History of other neoplasm	18 (22)	32 (20)	n.s.
Tumor site			
Proximal	52 (64)	82 (52)	n.s.
Distal	26 (32)	40 (25)	n.s.
Diffuse	3 (4)	37 (23)	0.0001
Entire pancreas along MPD	3 (4)	0	
Multifocal lesions	0	37 (23)	
Incidental diagnosis	11 (13.5)	55 (34.5)	0.0001
Abdominal pain			
Yes	45 (53)	72 (45)	n.s.
No	38(47)	87 (55)	
Presence of other symptoms[a]			
Yes	59 (73)	72 (45)	0.0001
No	22 (27)	87 (65)	
Jaundice	14 (17)	7 (5)	0.001
Diabetes	10 (12)	14 (9)	n.s.
Weight loss	41 (50.5)	37 (23)	0.0001
Acute pancreatitis	14 (17)	27 (17)	n.s.
Pathology			
Adenoma	9 (11)	71 (44)	0.0001
Borderline	17 (21)	54 (34)	0.05
Carcinoma *in situ*	16 (20)	17 (11)	n.s.
Invasive carcinoma	39 (48)	17 (11)	0.0001
Presence of lymph node metastases[b]	13 (33)	4 (23.5)	n.s.

[a]Some patients complained of more than 1 symptom; [b]Rate of lymph node metastases was calculated considering only patients with invasive intraductal papillary mucinous carcinomas. IPMNs: Intraductal papillary mucinous neoplasms; MD: Main-duct; BD: Branch-duct.

All these patients underwent surgical resection and therefore a histological diagnosis was available. Interestingly, combined-IPMNs showed close overlapping similarities with MD-IPMNs with regard to clinico-pathological and epidemiological characteristics. For example we found that MD-IPMNs and combined-IPMNs have the same sex ratio (female 44%, male 54%) opposite to that of BD-IPMNs. While the median age at presentation was similar in the three groups, patients with MD-IPMNs and combined-IPMNs with invasive cancer were significantly older than those with noninvasive neoplasms, suggesting tumor progression. As previously described, BD-IPMNs were more likely asymptomatic whereas the majority of patients with MD-IPMNs and combined-IPMNs were symptomatic. Finally, most patients with BD-IPMNs had an adenoma (44%) with a low prevalence of cancer (overall malignancy 22%, invasive cancer 11%). On the other hand, MD-IPMNs and combined-IPMNs contained malignant elements in 68% and 62% respectively, with invasive cancer present in 48% and 42%. Considering all these findings, we conclude that combined-IPMNs can be considered a sub-group of MD-IPMNs. The presence of an age difference between non-invasive and invasive tumors and the high frequency of malignancy in MD-IPMNs and combined-IPMNs[10,18,20] suggest that these IPMNs subtypes share an aggressive biology characterized by progression to invasive cancer.

ADVANCES IN PATHOLOGY

Based on morphological criteria and mucin expression, IPMNs can be classified in four subtypes including gastric, intestinal, pancreatobiliary and oncocytic types[6,27]. Ban *et al*[28] evaluated the features of 80 gastric-type IPMNs and of 30 with intestinal-type. They showed that gastric-type IPMNs were mostly BD-IPMNs (98%) and were associated with high-grade dysplasia or invasive cancer in only 8% of cases whereas the intestinal-type IPMNs were usually MD-IPMNs (73%) and had malignancy in 80% of cases. They also showed that intestinal-type IPMNs were characterized by MUC2 expression and that low-grade PanIN complexes were typical features of gastric-type IPMNs. These authors concluded that gastric and intestinal-type IPMNs have distinct histopathological features and mucin profiles, perhaps suggesting that they follow different biological pathways. This in turn may account for the clinical differences between BD-IPMNs and MD-IPMNs.

Unfortunately, specific genetic analysis in order to elucidate differences in the biological behavior among MD-IPMNs, BD-IPMNs and combined-IPMNs has not been published yet.

DIFFERENCES IN MANAGEMENT

Briefly, the differences in clinical-pathological characteris-

tics, risk of malignancy and biological behavior between MD-IPMNs (including the combined-type) and BD-IPMNs have a strong impact on their clinical management. Considering the high prevalence of malignancy/invasive carcinoma in MD-IPMNs and the lack of clinical and radiological parameters predictive of malignancy, all of these lesions in surgically fit patients have to be resected[6,10,16-19]. On the other hand, several studies demonstrated that BD-IPMNs less than 3 cm in size, without nodules and with no symptoms can be carefully managed in a surveillance program whereas surgical resection is indicated for any symptomatic lesion, for BD-IPMNs with a median diameter more than 3 cm and in the presence of nodules because these parameters are more frequently associated with a potential risk of malignancy[6,8,9,10-15].

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TOPIC HIGHLIGHT

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Extent of surgical resections for intraductal papillary mucinous neoplasms

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Abstract

Intraductal papillary mucinous neoplasms (IPMNs) can involve the main pancreatic duct (MD-IPMNs) or its secondary branches (BD-IPMNs) in a segmental of multifocal/diffuse fashion. Growing evidence indicates that BD-IPMNs are less likely to harbour cancer and in selected cases these lesions can be managed non operatively. For surgery, clarification is required on: (1) when to resect an IPMN; (2) which type of resection should be performed; and (3) how much pancreas should be resected. In recent years parenchyma-sparing resections as well as laparoscopic procedures have being performed more frequently by pancreatic surgeons in order to decrease the rate of postoperative pancreatic insufficiency and to minimize the surgical impact of these operations. However, oncological radicality is of paramount importance, and extended resections up to total pancreatectomy may be necessary in the setting of IPMNs. In this article the type and extension of surgical resections in patients with MD-IPMNs and BD-IPMNs are analyzed, evaluating perioperative and long-term outcomes. The role of standard and parenchyma-sparing resections is discussed as well as different strategies in the case of multifocal neoplasms.

Key words: Transection margin; Total pancreatectomy; Left pancreatectomy; Parenchyma-sparing resections; Intraductal papillary mucinous neoplasms; Follow-up; Diabetes; Pancreaticoduodenectomy; Exocrine insufficiency

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INTRODUCTION

The diagnosis of intraductal papillary mucinous neoplasms of the pancreas (IPMNs) has increased markedly in the last decade thanks to the widespread use of high-resolution imaging[1,2]. Nowadays they represent one of the most common indications for pancreatic resection at high-volume centers. IPMNs can be classified into main-duct (MD-IPMNs), including combined-IPMNs, and branch-duct type (BD-IPMNs), depending on the type of involvement of the ductal system of the pancreas[2]. It is well known that IPMNs encompass a spectrum of lesions from adenoma to invasive carcinoma, being considered as precancerous lesions, and that these neoplasms often involve the entire pancreas in a diffuse or multifocal fashion[2-5]. In this light, some authors have hypothesized that IPMNs represent a "field defect" that may involve the whole gland, clinically or subclinically[6]. From a surgical standpoint, there are three questions of importance to be

answered: (1) when to resect an IPMN; (2) which type of resection should be performed; and (3) how much pancreas should be resected. Surgical resection allows eradication of IPMNs, and should be tailored to the tumor topography in order to perform as complete a resection as possible, weighting the risk of tumor recurrence with the morbidity associated with extended resections as well as with the risk of postoperative pancreatic insufficiency. However, preoperative imaging is not completely reliable for evaluating the degree of tumor extension along the pancreas, and the intraoperative examination of the transection margin is of crucial importance to determine whether or not extend the resection up to total pancreatectomy[2,6-9].

Aim of this paper is to analyze the type and extension of surgical resections in patients with MD-IPMNs and BD-IPMNs, evaluating perioperative and long-term outcomes, and the role of standard and parenchyma-sparing resections.

MANAGEMENT OF MAIN-DUCT INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS

Indications for surgery

In patients with MD-IPMNs, the presence of a main pancreatic duct > 10 mm in size, mural nodules, and symptoms (new onset or worsening diabetes, steathorrea, jaundice, and weight loss) are all significant predictors of malignancy[2-4,10,11]. However, Sugiyama *et al*[12] have reported malignancy in the absence of mural nodules and dilated main duct, while Salvia *et al*[4] showed that 29% of patients with malignant MD-IPMNs are asymptomatic. In this setting, reliance on clinical and radiological parameters can not safely exclude malignancy. Moreover, the frequency of malignancy (*in-situ* and invasive carcinoma) in MD-IPMNs is high, ranging between 60% and 92% with a mean of 70%[2-4,10,11], and different series showed MD-IPMNs with noninvasive tumors may progress to malignancy[4,10]. For all these reasons, the current recommendation is that all MD-IPMNs, including the combined type, should be resected[2].

Type of surgical resection

The surgical management of main-duct IPMNs represents a unique challenge to the surgeon, because the preoperative localization of a main-duct IPMN may be difficult. High-resolution imaging (CT, MRCP) may show a dilated main pancreatic duct with or without cysts, intraductal masses or nodules. Dilation can involve a segment or the entire main pancreatic duct. This may be related to the neoplasm since MD-IPMNs can spread along the entire duct, but it might also occur both proximal and distal to the tumor because of overproduction of mucus and/or associated chronic pancreatitis. In consideration of tumor site and extension, a typical resection with lymph node dissection should represent the treatment of choice[2].

Nowadays pancreaticoduodenectomy (PD) and left pancreatectomy with splenectomy (LP) can be performed safely, and are associated with low mortality and acceptable morbidity in high-volume centers[13-15]. These procedures result in the removal of normal pancreatic tissue, leading to long-term exocrine/endocrine impairment. In the absence of chronic pancreatitis the incidence of postoperative diabetes ranges from 10% to 24 % after PD and from 8% to 60% after LP[16-22]. PD result in exocrine insufficiency in 30%-60% of patients, while LP is associated with exocrine insufficiency in up to 40% of cases, depending on the extent of resection[17-20,23,24].

Surgical strategy can be changed based on intraoperative findings (i.e. transection margin, see below), and extension of surgical resection up to total pancreatectomy may be required[2,4,7,8]. When a significant dilatation of the main pancreatic duct is present along the entire gland, a total pancreatectomy (TP) should be considered as the first surgical choice, especially if predictors of malignancy are evident at preoperative imaging (i.e. mural nodules). In the case of diffuse dilatation of the duct but with a diameter < 1 cm and with no mural nodules, the surgeon can initially perform a partial pancreatectomy, evaluate the surgical margin and, if necessary further extend the resection up to a TP, in the same procedure.

The decision to perform TP should be made following consideration the surgical risk and long-term complications associated with the procedure, and needs to be carefully balanced with factors such as patient age, presence of co-morbidities and of preoperative diabetes. In the past, TP led to obligate diabetes mellitus with frequent hypoglycaemic episodes[25-27] as well as the development of severe malabsorption due to exocrine insufficiency[25-29]. Moreover the procedure was associated with significant mortality and morbidity. However in the last two decades the management of patients undergoing TP has improved. Insulin-dependent diabetes and malabsorption are better controlled with new drugs and, in recent series, mortality and morbidity after TP are 5% and 30%-40% respectively, with acceptable quality of life[28-31]. At the University of Verona, total pancreatectomy was performed in 65 patients with no mortality and morbidity of 38.5%; planned-elective total pancreatectomy was performed in 14 (21.5%) patients with IPMNs, while other nine (14%) underwent total pancreatectomy after an initial partial pancreatectomy for a positive resection margin.

Parenchyma-sparing resections, such as middle pancreatectomy (MP), offer the advantage of sparing pancreatic parenchyma and preserving exocrine and endocrine function. On the other hand MP is associated with a high rate of complications, particularly pancreatic fistula. Roggin *et al*[16] in a review of 207 patients from 16 series who underwent MP reported an overall morbidity rate of 33% and a fistula rate of 22%. In the combined experience of the University of Verona and of the Massachusetts General Hospital with a series of 100 MPs, overall morbidity was 58% with no mortality or reoperation and the rate of clinically significant pancreatic fistula was 17%. In relation to

Table 1 Mortality, morbidity and long-term functional outcomes after different pancreatic resections

Procedure	Mortality (%)	Morbidity (%)	Exocrine insufficiency (%)	Endocrine insufficiency (%)
Pancreaticoduodenectomy	< 3	30-40	30-60	10-24
Left pancreatectomy	< 1	20-30	0-40	10-60
Total pancreatectomy	< 5	30-40	100	100
Middle pancreatectomy	< 1	40-60	< 5	< 4
Enucleation	< 1	40-60	< 2	< 2

long-term functional results, MP is an effective procedure to preserve pancreatic function. In our experience, after a median follow-up of 54 mo, the incidence of endocrine and exocrine insufficiency after MP was 4% and 5%, respectively[32] and similar results were reported by others[16,33,34]. In another study we evaluated the development of pancreatic insufficiency in 162 patients with benign tumors who underwent standard and parenchyma-sparing resections[35]. The probability of developing both endocrine and exocrine insufficiency was higher for PD and DP than for MP and enucleation (58%, 29% and 3% at 5 years).

However, from an oncological standpoint, the role of MP in treating MD-IPMNs is debatable[2]. In our experience, of six patients with MD-IPMN who underwent MP, four had positive resection margins at final histological examination and two of them recurred[32]. Blanc and colleagues reported more favorable results in patients with noninvasive IPMN[36]. It is notable that in MP there are two resection margins, and both must carefully evaluated intraoperatively. In case of positive resection margin(s) MP should be converted into standard pancreatic resection. However, considering the high rate of malignancy in MD-IPMNs, standard pancreatectomies should be the preferred treatment in this setting. Table 1 shows the rate of morbidity, mortality and pancreatic insufficiency according to different pancreatic resections.

In recent years, laparoscopic pancreatic resection techniques have been developed[37-41]. Early reports suggest that laparoscopic pancreatic surgery can be accomplished with acceptable morbidity and mortality for the resection of small benign and low-grade malignant lesions in the body and tail of the pancreas[37-41]. Laparoscopic distal pancreatectomy is associated with a similar morbidity to open LP, but with shorter length of hospital stay and faster recovery. Interestingly Baker *et al*[42] showed in a prospective study that laparoscopic LP failed to provide a lymphadenectomy comparable to open LP. Therefore further studies are needed to evaluate the role of laparoscopic resection for malignant IPMNs, and at the moment an "open" approach should be attempted.

Role of the transection margin

Intraoperative examination of the transection margin is of paramount importance in the management of MD-IPMNs[2-11]. Surgical margins in IPMN can be classified as negative (normal epithelium or mucinous hyperplasia without dysplasia in the main duct) or positive for adenoma, borderline neoplasm, or carcinoma. The IAP guidelines for the management of IPMNs suggest that when adenoma or low-grade PanIN lesions are found intraoperatively in a resection margin, no further resection is needed, but that the presence of borderline neoplasm, high-grade dysplasia or invasive carcinoma requires an extension of the surgical resection to a negative margin, up to a total pancreatectomy[2]. Finally, the presence of denudation, namely de-epithelialized ducts at the pancreatic margin, is not uncommon. In our experience denudation should be considered as a positive resection margin since local recurrence can occur[9,43]. Recently Partelli *et al*[44] showed in a cohort of 104 patients with invasive IPMNs, that the presence of denudation was associated with worse prognosis at univariate analysis. In this series, 12 patients (11.5%) showed denudation at final histological examination and 5 of 12 had a recurrence in the pancreatic stump, 4 in the liver and only 3 were free of disease during follow-up. The detection of denudation on frozen section examination should lead the surgeon to extend the resection[44].

In our experience with 140 patients affected by MD-IPMNs who underwent surgical resection, the surgical margins were negative in 72% of patients who had a partial pancreatectomy and in all cases the definitive examination of the transection margins confirmed the intraoperative diagnosis. The results of the intraoperative frozen section analysis modified the surgical plan in 29 patients (21%), leading to an extension of the resection or to total pancreatectomy[4]. Couvelard *et al*[43] studied frozen sectioning (FS) in a group of 127 patients who underwent partial pancreatectomy for IPMNs with a total of 188 FS. Definitive examinations corroborated FS in 176 of 188 cases (94%) and overall, 54 of 188 (29%) FS comprised at least IPMN adenoma on the transection margin leading to 46 further resections in 38 patients (30%). Conflicting results between FS and definitive examination resulted in inadequate extent of the resection in only four patients (3%)[43].

MANAGEMENT OF BRANCH-DUCT INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS

Indications for surgery

BD-IPMNs are associated with malignancy in about 25% of cases, and parameters associated with the presence of a malignancy are the presence of symptoms, bigger lesions (> 3 cm) and of mural nodules[2,5,6]. When these criteria are present, surgical resection is indicated not only to alleviate symptoms but also because of the higher likelihood of malignancy. On the other hand, current guidelines rec-

ommend a non-operative management for asymptomatic patients with BD-IPMNs less than 3 cm in size and without nodules[2].

Surgical treatment

Most BD-IPMNs require standard pancreatic resections. However MP can be an appropriate procedure for BD-IPMN < 3 cm in size in the neck of the pancreas and without malignancy features[32]. The intraoperative frozen section of the resection margins is less important for BD-IPMNs, except in the case of a malignant tumor or when there is concern about possible incomplete resection because of the proximity of the cyst to the margin or involvement of the main pancreatic duct[2]. At final histopathological examination it is important to rule out an extension of the IPMN from the BDs to the main pancreatic duct, because "combined" IPMNs show the same biological behavior as MD-IPMNs. Laparoscopic LP and spleen-preserving procedures should also be considered in patients with noninvasive BD-IPMNs.

Management of multifocal branch-duct intraductal papillary mucinous neoplasms

Multiple BD IPMNs along the gland (multifocal disease) can be demonstrated in a significant number of patients[2,45]. They constitute a challenge, since extended resection up to total pancreatectomy can be necessary to treat this disease[5,46].

In our experience with 145 resected BD-IPMNs, 25.5% of the patients had multifocal BD-IPMNs with no differences between benign (25%) and malignant (28%) neoplasms[5]. Schmidt *et al*[11] reported multifocal BD-IPMNs in 41% of their patients and that unifocal BD-IPMNs were invasive in 18% whereas multifocal lesions were invasive in only 7%. The appropriate management of these patients is still under debate and there are no specific guidelines. At the moment we suggest surgical resection only for symptomatic patients or for those with radiological findings associated with malignancy. For multifocal diseases that skip the body of the gland - including BD-IPMNs - we have recently proposed a parenchyma-sparing operation consisting of a middle-preserving pancreatectomy (MPP)[47]. With this procedure a total pancreatectomy can be avoided, and exocrine and endocrine pancreatic functions preserved in younger patients.

ROLE OF LYMPHADENECTOMY

A standard lymphadenectomy should be performed during resections for IPMNs, especially if malignancy is suspected. The rate of lymph-node metastases in patients affected by malignant IPMN ranges from 16% to 46%[2,11]. Sohn *et al*[10] and D'Angelica *et al*[48] showed that lymph-node status was predictive of survival in a univariate model. Recently we have evaluated the combined experience of the University of Verona and of the Massachusetts General Hospital with 104 IPMN patients with invasive carcinoma (88 MD-IPMNs and 16 BD-IPMNs) who underwent surgical resection[44]. Forty-two percent of these patients had lymph node metastases with a median number of 15 resected/evaluated nodes. Patients with lymph node metastases had a shorter 5-year disease-specific survival (28.9% *vs* 80.3%, $P < 0.05$). Interestingly we found that lymph node ratio (LNR) was a significant predictor of survival in invasive IPMNs, with 5-year survival significantly decreasing as the LNR increased. The potential benefit of a more extensive lymphadenectomy remains speculative and should be probably explored in a prospective trial.

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TOPIC HIGHLIGHT

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Role of frozen section assessment for intraductal papillary and mucinous tumor of the pancreas

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Abstract

Intraductal papillary mucinous neoplasms (IPMN) of the pancreas include a spectrum of dysplasia ranging from minimal mucinous hyperplasia to invasive carcinoma and are extensive tumors that often spread along the ductal tree. Several studies have demonstrated that preoperative imaging is not accurate enough to adapt the extent of pancreatectomy and have suggested routinely using frozen sectioning (FS) to evaluate the completeness of resection and also to check if ductal dilatation is active or passive, in order to avoid an excessive pancreatic resection. Separate main duct and branch duct analysis is needed due to the difference in the natural history of the disease. FS accuracy averages 95%. Eroded epithelium on the main duct, severe ductal inflammation mimicking dysplasia and reactive epithelial changes secondary to obstruction can lead to inappropriate FS results. FS results change the planned extent of resection in up to 30% of cases. The optimal cut-off leading to extend pancreatectomy is not consensual and our standard option is to extend pancreatectomy if FS reveals: (1) at least IPMN adenoma on the main duct; or (2) at least borderline IPMN on branch ducts; or (3) invasive carcinoma. However, the decision to extend resection must be taken after a multidisciplinary discussion since it does not exclusively depend on the FS result but also on age, general condition and expected prognosis after resection. The main limitation of using FS is the existence of discontinuous ("skip") lesions which account for approximately 10% of IPMN in surgical series and can lead to reoperation in up to 8% of cases.

Key words: Intraductal papillary and mucinous tumor; Pancreas; Frozen section; Branch duct; Dysplasia; Main duct

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INTRODUCTION

Intraductal papillary mucinous neoplasms (IPMN) include a spectrum of dysplasia ranging from minimal mucinous hyperplasia to invasive carcinoma and are extensive tumors that often spread along the ductal tree[1-3].

Several studies have demonstrated that preoperative morphological assessment is not accurate enough to adapt the extent of pancreatectomy and have suggested routine use of frozen sectioning (FS) for this purpose[4-8]. This review is based on the pertinent literature and on the surgi-

cal and pathological experience of a single institution. We will first discuss the technical aspects of FS in surgery for IPMN. Since the surgical management of IPMN includes several procedures ranging from enucleation to total pancreatectomy, we will discuss successively the role and value of FS in each surgical technique. Finally, we expose the limitations and pitfalls of FS in this indication.

SURGICAL AND PATHOLOGICAL TECHNIQUE

The most frequent type of surgery is partial pancreatectomy, usually pancreaticoduodenectomy (PD) which accounts for about 60% of cases in surgical series[6,8,9].

How should the surgeon manage the sample for frozen section?

Since diagnosis of IPMN is given by preoperative imaging in almost all cases, the need for FS and its implication in surgical strategy is known before surgery.

FS is performed either on the resected specimen or on a fresh slice of pancreatic cut surface harvested immediately after neck transection. In the latter setting, FS results can be obtained more rapidly during the procedure, thus allowing additional partial pancreatic resections and additional FS if needed. This may greatly reduce the length of surgery. In this setting, the surgeon must orientate the margin by guide mark stitches and identify the main duct if some branch ducts appear dilated.

All pancreatic transections for FS should be performed with a scalpel instead of electrocautery. The presence of either mucus or main duct dilatation at the level of transaction is not sufficient to indicate an additional pancreatic resection before the pathological results of FS[4]. In our opinion, it is not sufficient to only harvest one rim of main duct for FS since grading of dysplasia must be also performed in branch ducts[8].

How should the pathologist manage the sample for frozen section?

The pathologist must be aware of the suspected diagnosis of IPMN because the management of the sample is specific. The main duct must be identified macroscopically either in the PD specimen by catheterization or on a separate pancreatic slice by guide marks put by the surgeon (Figure 1). In addition, when the pancreatic slice is given separately, the side to be analyzed must have been indicated by the surgeon. The pathologist can ink the main duct to allow its definitive identification on histology because main duct lesions do not have the same clinical implication as branch duct lesions.

If the whole specimen has been also sent by the surgeon, it can be interesting to analyze its gross aspect and, if an area of possible malignant transformation which was not suspected by preoperative work-up is identified, it can be analyzed by FS, thus helping in the decision to perform an additional resection.

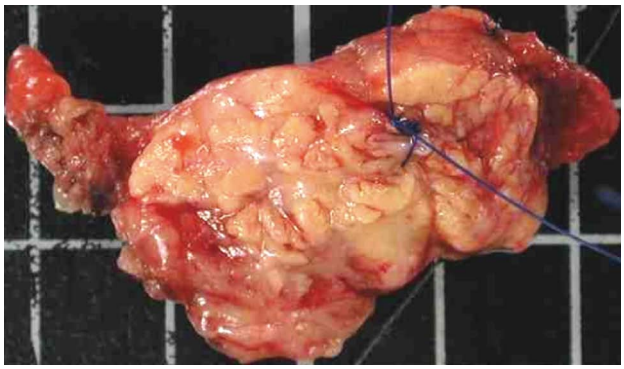

Figure 1 A fresh cut section just before frozen sectioning. The surgeon has orientated the margin by a guide mark stitch placed on the main duct.

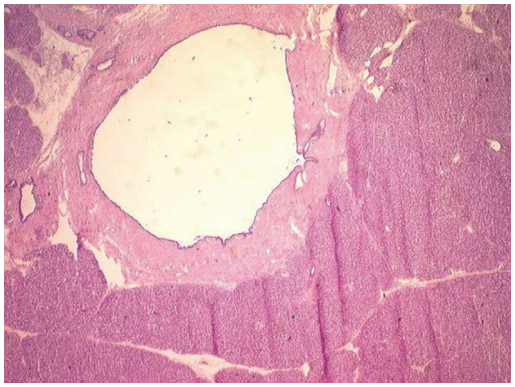

Figure 2 On this frozen section, the main duct is dilated but its epithelium is normal without any intraductal papillary mucinous neoplasms lesion.

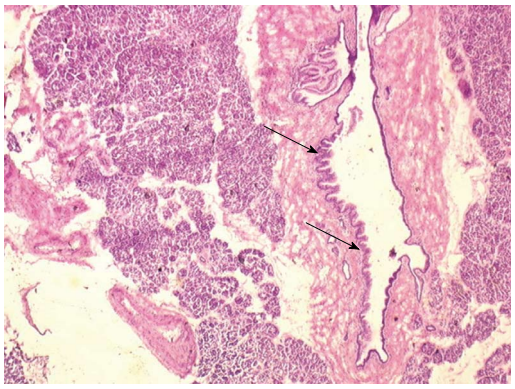

Figure 3 The main duct is focally involved by a low grade dysplastic intraductal papillary mucinous neoplasms (intraductal papillary mucinous neoplasms-adenoma) (arrows).

One 5 μm section is cut in a cryostat at -20℃, dried and colored by hematoxylin-eosin, mounted and analyzed under light microscopy. In case of eroded epithelium, several seriated sections are analyzed. The FS result includes description of both main duct and branch-ducts epithelium which can be normal or can include dysplastic changes ranging from low grade to high-grade dysplasia (Figures 2 to 4). Moreover, foci of invasive carcinoma are noted. In most cases, when the largest diameter of the sample is greater than 2 cm, it should be divided in

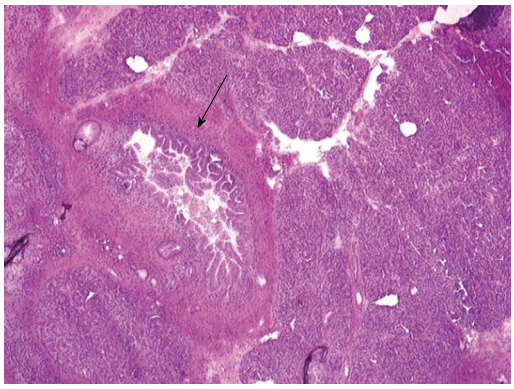

Figure 4 A borderline/moderate dysplasia intraductal papillary mucinous neoplasms involves a branch-duct (arrow). The surrounding pancreatic parenchyma is normal.

two pieces after precise identification of the main duct in order to preserve the integrity of its wall. Histological diagnosis of dysplasia can be challenging, particularly in case of associated inflammation or pancreatitis. This diagnosis necessitates optimization of technical conditions, especially when the specimen is large and/or when fatty infiltration is present; for this purpose it may be useful to perform at least two or three seriated 5 μm sections.

Because of the frequent coexistence of various degrees of epithelial atypia, lesions are categorized in each type of duct (i.e. main duct and branch ducts) according to the most severe degree of dysplasia observed[8].The frozen-sectioned fragment is systematically fixed in formalin 10%, embedded in paraffin and analyzed for definitive histology.

Transmission of frozen section results

The FS result must be transmitted by phone to the senior surgeon and written in both the pathological and the operative reports. Indeed, transmission of the FS result, if inaccurate, can be a source of inappropriate extent of pancreatic resection[8]. The decision not to extend resection or to perform an additional partial pancreatic resection must be consensual. If an additional pancreatic resection is needed, a subsequent FS is performed on the orientated additional specimen with the same protocol.

ROLE AND VALUE OF FROZEN SECTION ACCORDING TO TYPE OF LESIONS AND SURGICAL PROCEDURE

The main reasons for performing FS examination are to evaluate the completeness of resection and also to check if ductal dilatation is active or passive, in order to avoid an excessive pancreatic resection.

In this paragraph, we will firstly discuss the value of FS according to the degree of dysplasia and the location of IPMN lesions in branch and/or main ducts. Then we will give the specificities according to the type of resection (i.e. PD, distal pancreatectomy, medial pancreatectomy, enucleation and total pancreatectomy).

These guidelines apply mainly to non invasive IPMN. Indeed, for IPMN with obvious malignant transformation, an hemi-pancreatectomy with lymphadenectomy is indicated, thus limiting discussion about the extent of pancreatic resection.

Guidelines to extend pancreatectomy: The standard option

There is no consensual agreement about the management of the residual pancreas according the pathological analysis of the pancreatic margin at FS. It well known that, in surgical series, the rate of invasive carcinoma in patients with IPMN involving the main duct is high, ranging from 45% to 57% *vs* 6% to 37% for branch-ducts IPMN[9-15]. Furthermore, the risk of malignant transformation also greatly depends on the topography (i.e. branch ducts versus main duct) of the lesions: indeed, the 5-year risk of malignant transformation is 63% and 15% in main duct and branch ducts lesions respectively[16]. As a matter of fact, branch-duct IPMN lesions are presently managed nonoperatively if asymptomatic and without morphological signs suggestive of malignant transformation[16-21]. Then, according to the above data, in our center we analyze separately the lesions in main-duct and branch ducts[8]. We treat even a minimal lesion involving the main duct by additional resection[8]. Conversely, we tolerate residual mild dysplasia limited to branch ducts since it can be hypothesized that branch-duct IPMN-adenoma which is left in place carries a very delayed risk of recurrent evolutive disease[16-19]. So, our standard option is to extend the pancreatectomy if FS reveals: (1) at least IPMN adenoma on the main duct; or (2) at least borderline IPMN on branch ducts; or (3) invasive carcinoma.

However, the decision to extend or not pancreatectomy does not exclusively depend on the FS result but also on age, general condition and presumed stage of the disease (malignant or benign). As a first example, the value of total pancreatectomy for invasive IPMN when the transection margin is involved by dysplasia is debated: some authors advocate extending pancreatectomy until a disease-free margin on the main pancreatic duct is obtained[22] but most others, considering that long-term prognosis is affected mainly by the invasive component, do not recommend extending the pancreatectomy in this setting provided there is no invasive disease on the margin[10,23-25]. As a second example, leaving IPMN adenoma in main duct may be acceptable in a high-risk patient while presence of high-grade dysplasia should in most cases lead to accept an additional resection.

Management of frozen sectioning according to the type of resection

Technical possibilities of extending the pancreatic resection greatly vary according to the different types of resection. Furthermore, consequences of pancreatic resections also vary between the different procedures and according to the size of the residual pancreas.

Pancreaticoduodenectomy: After PD, the risk of *de novo*

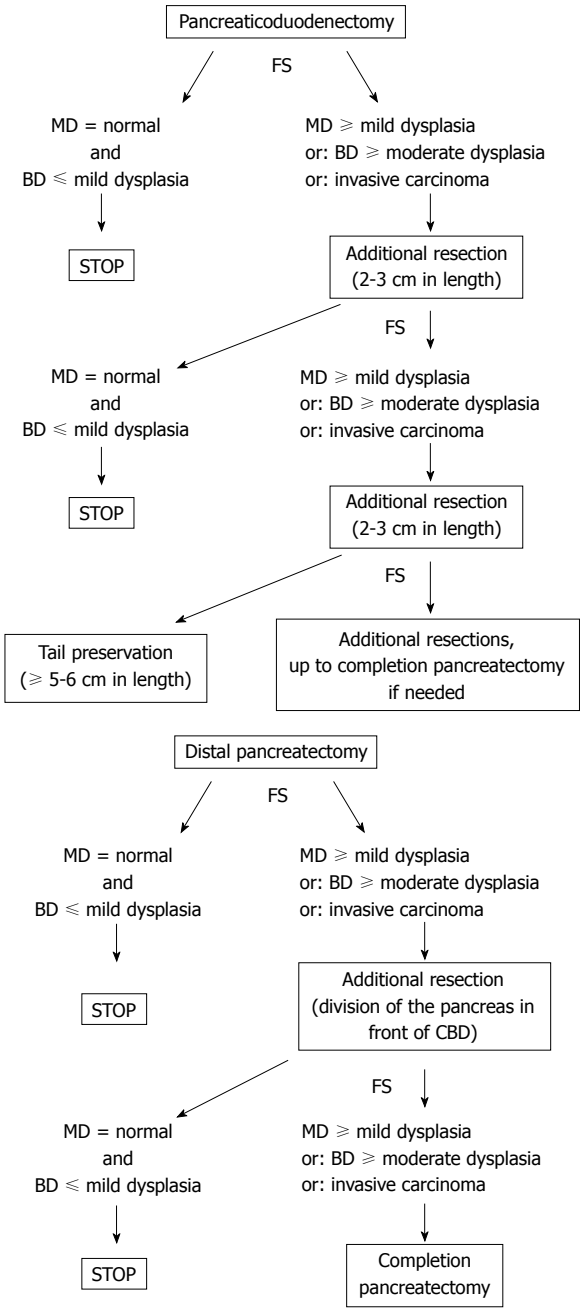

Figure 5 Standard options to determine extent of pancreatectomy according to results of frozen sectioning of the pancreatic margin after pancreaticoduodenectomy and distal pancreatectomy. FS: Frozen sectioning; MD: Main duct; BD: Branch duct; CBD: Common bile duct).

diabetes after PD is low, ranging from 0 to 7%[26-28]. Some patients keep a normal endocrine function with a 5 to 6 cm pancreatic remnant limited to the tail. Lastly, since IPMN usually predominates in the right pancreas or is limited to this side[6,8,9], it is possible in most cases to perform a complete resection.

According to these data, when the FS result on the pancreatic neck indicates to extend the resection, we recommend to remove a 2 to 3 cm additional pancreatic segment (progressively separated from the splenic vessels with ligature of their collaterals) and to check to the new transection margin by additional FS; if needed, a third or even fourth additional pancreatic resection can be performed (Figure 5). The pancreatic tail can be preserved and anastomosed to the digestive track if its length is at least 5 to 6 cm to ensure a significant endocrine function[29,30]. If the residual is less than 5 cm, three options are possible: (1) to try to perform an anastomosis which can be technically difficult with an uncertain long-term benefit; (2) to suture the margin and leave in place the remnant tail which can lead to a prolonged pancreatic fistula; and (3) to remove it, thus avoiding postoperative pancreatic complications but leading to a pancreatoprive diabetes. The former option can be chosen if the patient is young and there is no suspicion of residual disease.

It must be underlined that the attitude of successive resections with iterative FS during PD can limit the risk of surgically induced diabetes and, at the most, the risk of total pancreatectomy while suppressing all "risky" epithelium. As a matter of fact, in our previous series of 90 PD with FS, at least two margins (from 2 to 4) were examined by FS in 37% of procedures. Also, of the 127 patients in whom a partial pancreatectomy with FS was planned, only 9 (7%) ultimately underwent total pancreatectomy[8].

Distal pancreatectomy: In selected cases, a very short resection (limited to the tail) can be performed. In this case, it is easy to extend the resection if indicated by the FS result. In contrast, if the whole distal pancreas has been removed with division of the neck, the possibilities of extending the pancreatectomy are limited. The head-neck junction can be resected with division of the pancreas at the anterior edge of the common bile duct (or slightly on its left) provided the gastroduodenal artery has been mobilized with division of its pancreatic collaterals or even resected. This creates a wider transsection margin with a likely higher risk of fistula but with another possibility of FS (Figure 5). If this latter margin is involved by IPMN lesions indicating an additional resection, this usually leads to complete the pancreatectomy by means of a PD provided the operative risk is low. Taking into account that IPMN lesions rarely predominate on the distal pancreas[6,8,9], the risk of completing pancreatectomy during distal pancreatectomy is low but may exist. For this reason, the patient should be aware of this possibility.

Medial pancreatectomy: The management of both margins analysis during medial pancreatectomy associates the analysis of each margin as performed for PD and DP[8,30]. However, especially if there is some suspicion of segmental involvement of the main duct, FS results on both margins should be known before any additional resection is started. As an example, finding mild dysplasia on the main duct of the left margin should not indicate necessarily to extend resection to the left if high-grade dysplasia is present on the right-margin which should imply to resect the pancreatic head.

Enucleation: In this indication, FS is performed in order to: (1) to check, as for other procedures, if the resection is complete. For this purpose, the communicating duct is

analyzed and is considered as a branch-duct with a cut-off tolerating only mild dysplasia as described above. Since the communicating dust is usually small in diameter (less than 1 mm), the surgeon must mark it with a stitch or give it separately; and (2) to exclude invasive malignancy which requires an oncological resection[31]. For this purpose, the cyst is opened by the pathologist who select a suspect area if present i.e. papillae, mural nodule or wall thickening. Since there is no strict correlation between gross aspect and histology in case of microinfiltrative adenocarcinoma, we recommend to routinely perform this analysis. Moreover, the histological grading of dysplasia in the cyst can help to analyze the communicating duct which is always limited in size.

Total pancreatectomy: In some patients, a total pancreatectomy is planned. However, it can be interesting to perform it as a two-step procedure event if it is more complicated. Indeed, passive dilatation associated with IPMN can mimic diffuse main duct involvement. Passive dilatation can be located upstream from a stenosis (usually due to invasive carcinoma) but also downstream from a mucin-producing lesion resulting in ductal dilatation towards the papilla.

VALUE OF FROZEN SECTION

There are very few series that report the value of FS during pancreatectomy for IPMN. In the series published by Falconi *et al*[6] in 2001, the margin was analyzed by frozen section without precision on the subtype of duct involved (i.e. main or branch duct); they considered as positive the margins harbouring high-grade dysplasia or invasive carcinoma. Fifty-one patients were included and definitive examination confirmed the result of FS in 100% of cases. Interestingly, they showed that the 4 patients who subsequently underwent reoperation for recurrence had deepithelialized duct at the margin of the first operation. Another experience published in 2007 and including 27 FS of pancreatic margins reported a predictive positive and negative value of 88% and 47% respectively[7].

In our series of 127 consecutive patients who underwent pancreatic resection for IPMN at our institution, the accuracy of FS for detection of "significant" lesions as defined above was 94% and the routine use of FS led to modify the planned resection in 30% of the patients[8]. This rate is comparable to the 23% rate of modification of the planned operation reported by Gigot *et al*[5]. Of our patients who had additional resection because of significant lesions at the first FS, 95% had IPMN lesions on the second resection specimen which demonstrated that the analysis of the margin is efficient to guide the extent of pancreatectomy in this disease.

Moreover, we highlighted in our study that the rate of "significant" lesions was greater in cases of IPMN involving the main duct (39% *vs* 15% in case of branch-duct IPMN, $P < 0.01$). The rate of significant lesions on the first analyzed FS was almost the same as if it was a PD or a left pancreatectomy (28%) but rose to 50% in case of planned medial pancreatectomy[8]. As reported by Wada *et al*[23], we found an eroded main-duct epithelium in 8% of cases. We then suggest this finding should routinely lead to an additional resection since it seems to be associated with recurrence in the pancreatic remnant.

During enucleation of branch-duct IPMN, accuracy of FS on the dilated duct and the communicating seems equivalent to that observed with analysis of a full pancreatic margin in our experience[31].

LIMITATIONS AND PITFALLS

In addition to eroded epithelium on the main duct that we discussed above, the presence of severe inflammation may wrongly mimic dysplasia by increasing cellular atypias. In contrast, duct dilatation harboring hyperplastic reactive epithelial changes secondary to obstruction or chronic pancreatitis may be wrongly interpreted as IPMN[2,24,32]. Recognition of these ductal lesions may avoid pancreatectomies with excessive extent.

The main limit of using FS to adapt extent of resection is the existence of discontinuous ("skip") lesions. Rate of discontinuous lesions ranges from 6% to 19% in surgical series[25,33,34]. However, it is well known that the degrees of dysplasia can vary in the same patient and it is likely that some tumors were classified as discontinuous even in case of areas of mild dysplasia separating areas with more severe lesions.

The main clinical consequence of skip lesions is the possibility of recurrence after partial pancreatectomy with normal transection margin[9,11,24]. Recurrence after resection for invasive IPMN is mainly due to the invasive component. Conversely, the rate of recurrence after partial pancreatectomy for non invasive IPMN is low, not exceeding 8% of cases[7,9,11,24]. In this setting, the rate of local recurrence seems higher when the margin is involved by IPMN lesions than when disease-free; in the study of White *et al*[7] this rate was 17% (4/23) and 3% (1/32) respectively.

To detect "skip" lesions, the only reported techniques are cytology of pancreatic juice harvested in the remnant in addition to FS and intraoperative wirsungoscopy with staged biopsies. In the study of Eguchi *et al*[34], 8 discontinuous IPMN were proven after analysis of the entire segments of resected pancreas at definitive histology. Among these eight, 5/8 (i.e. 5/43 = 12% of the whole series) had been detected by the only result of intraoperative cytology. Intraoperative wirsungoscopy with staged biopsies has only been reported by a few groups[5,35]; probably because this technique is only suitable for detection of main duct lesions provided the main duct is dilated.

CONCLUSION

In conclusion, FS is a necessary tool for the surgical management of IPMN and should be used routinely. Although the optimal cut-off leading to extend pancreatectomy is not consensual, FS is helpful to evaluate the completeness

of resection and also to check if ductal dilatation is active or passive, in order to avoid an excessive pancreatic resection. Separate main duct and branch duct analysis seems convenient, due to the difference in natural history of the disease. To be accurate, FS needs an optimal technique from the surgeon and the pathologist. The decision not to extend resection or to perform an additional partial pancreatic resection must be taken after a multidisciplinary discussion since it does not exclusively depend on the FS result but also on age, general condition and the expected prognosis after resection.

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TOPIC HIGHLIGHT

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Prognosis of invasive intraductal papillary mucinous neoplasms of the pancreas

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Abstract

Intraductal papillary mucinous neoplasms (IPMN) are mucin producing cystic neoplasms of the pancreas histologically classified as having non-invasive and invasive components. The five-year survival rates for non-invasive and associated invasive carcinoma are 90% and 40%, respectively in resected IPMN lesions. Invasive carcinoma within IPMN lesions can be further classified by histological subtype into colloid carcinoma and tubular carcinoma. Estimated five-year survival rates following resection of colloid carcinoma range from 57%-83% and estimated five-year survival following resection of tubular carcinoma range from 24%-55%. The difference in survival outcome between invasive colloid and tubular IPMN appears to be a function of disease biology, as patients with the tubular subtype tend to have larger tumors with a propensity for metastasis to regional lymph nodes. When matched to resected conventional pancreatic adenocarcinoma lesions by the Memorial Sloan Kettering Cancer Center pancreatic adenocarcinoma nomogram, the colloid carcinoma histological subtype has an improved estimated five-year survival outcome compared to conventional pancreatic adenocarcinoma, 87% and 23% (P = 0.0001), respectively. Resected lesions with the tubular carcinoma subtype overall have a similar five-year survival outcome compared to conventional pancreatic adenocarcinoma. However, when these groups were stratified by regional lymph node status patients with negative regional lymph nodes and the tubular subtype experienced significantly better survival than patients with a similar nodal status and ductal adenocarcinoma with estimated five-year survival rates of 73% and 27% (P = 0.01), respectively.

Key words: Intraductal papillary mucinous neoplasms; Pancreatic adenocarcinoma; Prognosis

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INTRODUCTION

Intraductal papillary mucinous neoplasms (IPMN) are mucin producing cystic neoplasms of the pancreas first recognized by the World Health Organization in 1996[1]. Dysplasia within these lesions is categorized as low grade, moderate grade and high grade[2]. Associated invasive carcinoma may be identified in 40%-60% of resected IPMN lesions with estimated five-year survival rates following complete resection approaching 40% in most reported series[3-5]. Estimated five-year survival rates are over 90% in non-invasive resected IPMN lesions[2,3].

Long-term survival following complete surgical resection for conventional pancreatic ductal adenocarcinoma is

historically poor with five-year survival rates ranging from 10%-20%[6,7]. Traditionally, patients with resected invasive IPMN are presumed to have a more favorable prognosis than patients resected for conventional pancreatic ductal adenocarcinoma[3,4]. Until recently, a paucity of patients and a lack of detailed histological subtype analysis have prevented a valid comparison of prognosis between patients with pancreatic adenocarcinoma arising in the setting of IPMN and conventional pancreatic ductal adenocarcinoma (unpublished data).

This article describes the current understating of outcomes following resection of pancreatic adenocarcinoma arising in the setting of IPMN and compares this to the reported survival outcomes of resected conventional adenocarcinoma. Survival following resection of invasive IPMN has been shown to be strongly influenced by histological subtype (colloid carcinoma and tubular carcinoma) and the differences between these two entities are highlighted.

PROGNOSIS BY CLINICOPATHOLOGICAL SUBTYPE

Two distinct histopathological subtypes of invasive IPMN have been described, colloid carcinoma and tubular carcinoma[8]. Tubular carcinoma arising in association with IPMN is similar in histological appearance to conventional pancreatic ductal adenocarcinoma with neoplastic cells arranged in small, tubular glands with associated desmoplastic invasion[8]. Colloid carcinoma arising in association with IPMN is characterized by an abundance of acellular matrix. By definition, colloid carcinoma has greater than 80% of the invasive component composed of extensive stromal pools of acellular matrix lined by or containing floating neoplastic epithelial cells[8].

Invasive colloid and tubular carcinoma present as two distinct histological entities and are presumed to arise from histologically distinct IPMN precursor lesions. Colloid carcinoma is generally identified in association with intestinal-type IPMN and tubular carcinoma is generally found in association with pancreatobiliary IPMN[9].

Immunohistochemical studies have identified differences in the expression of the glycoproteins, MUC1, MUC2 and CDX2, between invasive colloid and tubular carcinoma IPMN, further suggesting that these entities are distinct from a molecular standpoint[10-12]. Colloid carcinoma associated with IPMN generally expresses both MUC2 and CDX2, markers of intestinal differentiation, a characteristic of more indolent carcinomas[13]. Tubular carcinoma associated with IPMN generally expresses MUC1, which is also generally expressed in conventional pancreatic ductal adenocarcinoma, but not MUC2 or CDX2[12-14]. Together these data suggest that colloid carcinoma arising in association with IPMN should be considered as a separate biological entity from tubular carcinoma associated with IPMN.

The characterization of invasive IPMN by histological subtype is also clinically relevant as patients with resected colloid and tubular carcinoma have significantly different disease-specific outcome. Multiple series have reported a more favorable outcome for colloid carcinoma compared

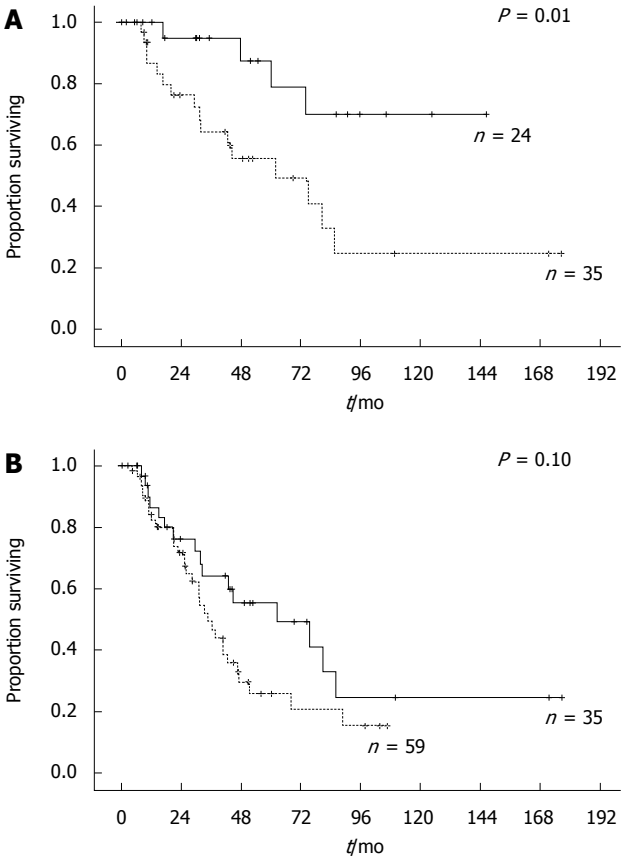

Figure 1 Kaplan-Meier estimated overall survival curves. A: Kaplan-Meier estimated overall survival curves of invasive colloid IPMN (soild line) and invasive tubular IPMN (dotted line); B: Kaplan-Meier estimated overall survival curves of invasive tubular IPMN (soild line) and conventional pancreatic ductal adenocarcinoma (dotted line).

to the tubular carcinoma subtype. Estimated five-year survival rates following resection of colloid carcinoma range from 57%-83% and estimated five-year survival following resection of tubular carcinoma range from 24%-55%[15-17]. In a previous report from the Memorial Sloan Kettering Cancer Center (MSKCC) the tubular carcinoma subtype had a worse prognosis and was associated with malignant regional lymph nodes and a disseminated recurrence pattern[4]. This initial series has been recently updated (data not published) and in this larger series of patients multivariate analysis identified the tubular carcinoma subtype and the presence of malignant regional lymph nodes to be the only factors predictive of decreased survival following resection of invasive IPMN (unpublished data). Figure 1A illustrates the association between histopathological subtype and survival. The five-year estimated survival rates for tubular carcinoma and colloid carcinoma were 55% and 87% ($P = 0.01$), respectively.

The difference in disease-specific survival outcome between invasive colloid and tubular IPMN appears to be a function of disease biology, as patients with the tubular subtype tend to have larger tumors with a propensity for metastasis to regional lymph nodes. These prognostic factors should be considered in the decision-making process regarding adjuvant therapy following resection of invasive IPMN, although because of the relative rarity of these

lesions no prospective data exist to assist in the decision regarding adjuvant therapy. In the updated MSKCC series noted above we favored the use of chemotherapy for patients with poor prognostic factors including malignant regional lymph nodes or tumor recurrence.

It is unclear if all patients with the tubular subtype should be considered for adjuvant chemotherapy, as there is clearly a subset of these patients that have a favorable disease biology and experience long-term survival. Patients with a tubular subtype, tumor size less than 1 cm and an absence of spread to regional lymph nodes experienced a three-year survival rate approaching 85%, nearly identical to the colloid carcinoma subtype. The role of adjuvant therapy in these patients is even more controversial than in the large node positive tubular lesions. Future studies with cohorts of patients characterized by histological subtype and prognostic factors will provide important recurrence and survival information to clarify the role of adjuvant radiotherapy and chemotherapy in resected invasive IPMN.

PREDICTORS OF INVASIVE INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS AND HISTOLOGICAL SUBTYPE

Several studies have described preoperative predictors of invasive carcinoma associated with IPMN, including the presence of mural nodules, tumor size > 3.5 cm, solid component and a significantly dilated pancreatic duct (> 10 mm) [18,19]. However, current imaging techniques lack sufficient sensitivity and radiological features to adequately distinguish between histological subtypes and future studies are needed to better define preoperative predictors of subtype. Routine laboratory values including serum CEA and CA19-9 also currently lack the sensitivity necessary to serve as a predictive biomarker of histological subtype. Recently we have shown that serum and pancreatic cyst fluid mucin levels are predictive of dysplasia in resected IPMN specimens[20]. Currently there is no role for tumor biopsy for histological subtyping of suspected IPMNs which could act as an aid to guide pre-operative management decisions.

COMPARISON TO CONVENTIONAL PANCREATIC DUCTAL ADENOCARCINOMA

Historically, reports have suggested improved outcomes for patients with resected invasive IPMN compared to patients who have undergone resection for conventional pancreatic ductal adenocarcinoma. Sohn *et al*[15] demonstrated that patients resected for invasive carcinoma in association with IPMN had a more favorable prognosis than patients resected for conventional pancreatic ductal adenocarcinoma. Estimated five-year survival following resection of invasive IPMN was 62% while the estimated five-year survival following resection of conventional pancreatic ductal adenocarcinoma was 19%[15]. This initial report however failed to stratify the invasive IPMN group by histological subtype. An updated series by Sohn *et al*[3] demonstrated that colloid carcinoma had a more favorable prognosis than tubular carcinoma although no comparison to conventional pancreatic ductal adenocarcinoma was carried out. This series, as well as an additional large series from MSKCC were limited with respect to duration of patient follow-up, overall patient numbers and a lack of a matched analysis[21-24]. The lack of stratification into the tubular and colloid histological subtypes may explain the general belief that invasive IPMN carries a more favorable prognosis than conventional pancreatic ductal adenocarcinoma. When stratification by histopathological subtype has been performed, the outcome of the tubular subtype has been generally similar to what is expected for conventional pancreatic ductal adenocarcinoma while the colloid subtype appears to have a significantly better prognosis[4].

The most recent update of the MSKCC experience with invasive IPMN sought to perform a carefully matched comparison of post-resection outcome in patients resected for conventional pancreatic ductal adenocarcinoma and invasive IPMN. Patients with invasive IPMN were matched to patients with conventional pancreatic adenocarcinoma through the use of a post-resection pancreatic adenocarcinoma nomogram developed by Brennan *et al*[25]. This validated nomogram predicts outcome more accurately than tumor stage and allows matching of relevant clinicopathological variables such as tumor size and nodal status through the use of an overall nomogram score. We prefer this approach because of the difficulty in matching T-stage within the IPMN group. AJCC guidelines currently define a pT_1 tumor as being between 0.1 to 2.0 cm diameter[21-24]. Therefore a patient with a 0.1 cm invasive IPMN could be compared to a 2.0 cm conventional pancreatic ductal adenocarcinoma despite evidence suggesting that tumor size is a strong predictor of regional lymph node status and overall survival. Given the proportion of patients who present with a < 1 cm focus of invasive IPMN, matching to this variable alone may favor the IPMN group.

The results of this matched analysis demonstrated that the colloid carcinoma subtype had a favorable prognosis compared to conventional pancreatic ductal adenocarcinoma. The estimated five-year survival outcomes for colloid carcinoma and ductal adenocarcinoma were 87% and 23% (P = 0.01) respectively. There was no difference in overall survival between the tubular subtype and ductal adenocarcinoma groups (Figure 1B). However, when these groups were stratified by regional lymph node status patients with negative regional lymph nodes and the tubular subtype experienced significantly better survival than patients with a similar nodal status and ductal adenocarcinoma, with estimated five-year survival rates of 73% and 27% (P = 0.01) respectively. Patients with positive regional lymph nodes had a similar outcome whether they had a tubular subtype or ductal adenocarcinoma. Regional lymph node status appears to be a surrogate marker of disease biology of invasive tubular IPMN.

CONCLUSION

The prognosis of invasive IPMN is strongly correlated to the histological subtype with favorable survival in patients with colloid carcinoma. Patients with resected invasive tubular IPMN should, on the whole, be expected to have a similar outcome as conventional pancreatic ductal adenocarcinoma, although patients with small, node negative lesions are likely to experience greater long-term survival. Although the role of adjuvant chemotherapy remains undefined these prognostic factors should be considered in the decision-making process.

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TOPIC HIGHLIGHT

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Extrapancreatic malignancies and intraductal papillary mucinous neoplasms of the pancreas

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Abstract

Over the last two decades multiple studies have demonstrated an increased incidence of additional malignancies in patients with intraductal papillary mucinous neoplasms (IPMNs). Additional malignancies have been identified in 10%-52% of patients with IPMNs. The majority of these additional cancers occur before or concurrent with the diagnosis of IPMN. The gastrointestinal tract is most commonly involved in secondary malignancies, with benign colon polyps and colon cancer commonly seen in western countries and gastric cancer commonly seen in Asian countries. Other extrapancreatic malignancies associated with IPMNs include benign and malignant esophageal neoplasms, gastrointestinal stromal tumors, carcinoid tumors, hepatobiliary cancers, breast cancers, prostate cancers, and lung cancers. There is no clear etiology for the development of secondary malignancies in patients with IPMN. Although population-based studies have shown different results from single institution studies regarding the exact incidence of additional primary cancers in IPMN patients, both have reached the same conclusion: there is a higher incidence of extrapancreatic malignancies in patients with IPMNs than in the general population. This finding has significant clinical implications for both the initial evaluation and the subsequent long-term follow-up of patients with IPMNs. If a patient has not had recent colonoscopy, this should be performed during the evaluation of a newly diagnosed IPMN. Upper endoscopy should be performed in patients from Asian countries or for those who present with symptoms suggestive of upper gastrointestinal disease. Routine screening studies (breast and prostate) should be carried out as currently recommended for patient's age both before and after the diagnosis of IPMN.

Key words: Intraductal papillary mucinous neoplasm; Secondary malignancy; Malignant potential; Invasive; Non-invasive

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INTRODUCTION

After the initial description of intraductal papillary mucinous neoplasms (IPMN) in the 1980s and the World Health Organization classification in 1996, both the recognition and incidence of this potentially malignant neoplasm have increased. IPMNs have been extensively

studied and much has been learned about the radiographic findings, behavior and clinical management of these unique neoplasms[1-3].

In the last two decades, multiple reports have suggested that patients with IPMNs have an increased risk of developing extrapancreatic malignancies when compared with the general population. These malignancies may occur before, concurrent with, or after the initial diagnosis of IPMN with the majority of cases being diagnosed before or concurrently. The increased incidence of additional malignancies in patients with IPMNs influences the preoperative evaluation and long-term follow up of these patients.

This review will examine the current literature on this topic. Specifically, we will discuss the timing of additional malignancies and the possible mechanisms involved in the development of secondary malignancies. In addition, we will identify individuals with other malignancies who are at potential high-risk for the development of IPMNs and discuss the clinical implications of these findings with respect to the preoperative evaluation and long-term follow up of patients diagnosed with IPMNs.

ETIOLOGY AND RISK FACTORS FOR EXTRAPANCREATIC MALIGNANCY

There is no clear etiology for the development of secondary malignancies in patients with IPMNs. It is possible that the increased incidence can be attributed to increased surveillance at the time of diagnosis of IPMN. This is supported by the fact that a large number of patients are diagnosed with coincident extrapancreatic malignancies after an IPMN has been identified. The diagnosis of IPMN may prompt additional testing such as colonoscopy, esophagogastroduodenoscopy (EGD), or further imaging, leading to an increase in the diagnosis of extrapancreatic malignancies but not the true incidence.

Few factors have been consistently associated with secondary malignancies in patients with IPMN. Several studies have shown that the patients with IPMNs and extrapancreatic malignancies are older than patients with IPMNs and no extrapancreatic malignancies[4-8]. A multivariate logistic regression analysis using Surveillance, Epidemiology, and End Results (SEER) data demonstrated increasing odds of extrapancreatic malignancy before or at the time of diagnosis of IPMN with increasing age group. When compared to patients less than 45 years, patients 55 to 64 were 2.1 (95% CI: 1.2-3.7) times more likely to have an extrapancreatic malignancy at or before the time of presentation. Patients 64-74, 75-84 and 85 years and older were 3.1 (95% CI: 1.9-5.3), 4.0 (95% CI: 2.4-6.7), and 3.5 times (95% CI: 2.0-6.0) more likely, respectively, to have an extrapancreatic malignancy. Patients who were female and white also had an increased risk of extrapancreatic malignancy, before, concurrent with, or after their diagnosis of IPMN[7].

There are likely to be common genetic risk factors which are as yet unidentified. In a recent study evaluating the gene expression in IPMN[9], no difference was found in *p53*, *p21*,*Bd-2* and *MUC5AC* expression for IPMNs associated with or not associated with extrapancreatic malignances. However, the authors did note increased expression of the intestinal-type secretory mucin (*MUC2*) gene in the IPMN population with extrapancreatic neoplasms. Further evidence of genetic predisposition is suggested by a case report of IPMN associated with familial adenomatous polyposis (FAP). In this case a mutation in the second allele of the *APC* gene initially identified in the primary colonic tumor was also found in the pancreatic IPMN, implying a common genetic mechanism[10].

These genetic studies identify two potentially high risk groups. Based on their data, Lee *et al*[9] recommend more intense screening for extrapancreatic malignancy in patients whose IPMNs are *MUC2* positive. In addition, patients with FAP may be at higher risk for development of IPMNs. Further studies are needed to make specific recommendations, although patients with FAP already undergo close surveillance. Identification of a pancreatic cystic lesion in this group should raise suspicion for IPMN especially in the setting of the identified mutation in the *APC* gene.

Patients with IPMNs may also share environmental risk factors for the development of extrapancreatic malignancies. Further genetic and environmental studies will be necessary to elucidate the etiology.

OVERVIEW OF PREVIOUS STUDIES

Sugiyama *et al*[11] in one of the first articles published about this topic, reported a 48% incidence of extrapancreatic malignancies in patients with IPMNs. Since then, nine additional studies have reported on the same topic. These studies are summarized in Table 1 including the total number of patients, frequency of extrapancreatic malignancies, percentage of patients with colon and gastric cancer, and the percentage of extrapancreatic malignancies occurring before or concurrent with the diagnosis of IPMN.

In the nine studies, the incidence of extrapancreatic malignancies ranged from 10% to 52%. In all studies the reported incidence of extrapancreatic malignancies exceeded the expected rate of such malignancies in the general population. With the exception of the study by Riall *et al*[7] all studies were single institution studies and included patients with both benign and malignant IPMNs. The Riall study was the only population based study and used data from the SEER Tumor Registry[7]. In addition, this study included patients with malignant (or invasive) IPMNs only, as benign IPMNs are not captured in SEER. Only three studies included patients that did not undergo surgery[7,12,13].

In all studies, the great majority of extrapancreatic neoplasms were diagnosed before or concurrent with the diagnosis of IPMN (range, 66%-94%). The Mayo Clinic study[13] did not evaluate the incidence of extrapancreatic malignancies after the diagnosis of IPMN. Each study

Table 1 Studies reporting extrapancreatic malignancies in patients with intraductal papillary mucinous neoplasm

Authors	Year	*n* (IPMN)	Frequency secondary malignancies (%)	Polyps (%)	Colon Ca (%)	Gastric Ca (%)	Dx before or with IPMN (%)
Reid-Lombardo *et al*[13]	2010	471[1]	52	24	4	0	100
Oh *et al*[6]	2009	37[2]	38	3	8	8	86
Baumgaertner *et al*[14]	2008	178[2]	17	NR	2	NR	70
Yoon *et al*[8]	2008	210[2]	34	NR	7	14	94
Ishida *et al*[15]	2008	61[2]	24	NR	8	10	93
Riall *et al*[7]	2007	992[3]	10	NR	3	0.1	86
Choi *et al*[4]	2006	61[2]	39	3	7	13	88
Eguchi *et al*[5]	2006	69[2]	42	NR	12	6	66
Kamisawa *et al*[12]	2005	79	35	NR	9	15	87.5
Sugiyama *et al*[11]	1999	42[2]	48	21	12	10	75

[1]Do not evaluate secondary malignancies after diagnosis of intraductal papillary mucinous neoplasm (IPMN); [2]Included patients with resected IPMNs only; [3]Population based. Invasive IPMNs only. NR: Not reported.

has varying lengths of follow up with a mean follow up between 14 and 50 mo after the diagnosis of IPMN. It is assumed that patients in all these studies are at the same increased risk for extrapancreatic malignancies after the diagnosis of IPMN. However, a low incidence is observed in some studies due to significantly shorter periods of follow-up after the diagnosis of IPMN. In addition, as half to one third of IPMNs in these reports are invasive, many patients go on to die from their IPMN-associated invasive cancer and therefore do not develop additional extrapancreatic malignances.

SITES OF EXTRAPANCREATIC MALIGNANCIES

The digestive system is the most common site for secondary malignancies associated with IPMNs. The types of additional cancers reported in patients with IPMNs reflect cancer patterns in the country in which the study was done. Colorectal cancers were the most common extrapancreatic malignancies associated with IPMN in studies performed in Western populations, ranging from 3% to 12%[7,13,14] while gastric cancers were reported in 6% to 15% of Asian patients with IPMNs[4-6,8,11,12,15]. The incidence of gastric cancers in Western studies was less than 1%[7,13]. Other GI malignancies reported in patients with IPMN include esophageal tumors, hepatobiliary tumors, carcinoid tumors, and gastrointestinal stromal tumors, although the rates are inconsistent among different studies. The Mayo Clinic group demonstrated a higher incidence of hepatobiliary (OR = 3.0, 95% CI: 1.1-8.1), esophageal (OR = 5.5, 95% CI: 1.8-16.5) and GI stromal tumors (OR = 3.8, 95% CI: 1.0-14.1) in patients with IPMNs when compared to a control population of patients referred to the Mayo Clinic for other problems[13].

In 2005, Eguchi *et al*[5] compared the incidence of colorectal cancer in patients with IPMN to the expected incidence in normal population and found that the observed to expected (O/E) ratio for colorectal cancer in patients with IPMN was 5.37. In the U.S., Riall *et al*[7], using the SEER database, found that the O/E ratio for colorectal cancer was 1.66 in patients with IPMNs. Reid-Lombardo *et al*[13] also report a similar O/E ratio of 1.6 (95% CI: 0.8-3.4) for the development of colon cancer when the IPMN group was compared with the matched-control group from the general population, although this difference did not achieve statistical significance in their study.

For those tumors that arise outside the GI system, breast and lung cancers have been associated with an increased O/E ratio in IPMN patients when compared to the general population[7,12]. Prostate cancer, renal cell carcinoma, lymphoma, thyroid cancer, and other cancers have been reported in patients with IPMNS, but most of these tumors are present in only a small proportion of patients and no clear association with IPMNs has been established[4,5,8,12-15].

In the Mayo Clinic study[13], it was found that IPMNs were not only associated with malignant neoplasms but, as one might expect, they were also associated with a statistically significant increase in the incidence of benign neoplasms. These benign neoplasms are precursors for the development of future malignancies including adenomatous colon polyps and Barrett's metaplasia of the esophagus. While they did not find a significant increased in colon cancer in IPMN, the incidence in colonic adenomas was significantly higher in patients with IPMNs than those with pancreatic ductal cancer (OR = 1.6, 95% CI: 1.2-2.3) or a control population from the Mayo Clinic (OR = 1.9, 95% CI: 1.4-2.4). A 21% prevalence of colon adenomas was also noted by Sugiyama and colleagues in their 1999 study[11].

DIFFERENCES IN POPULATION-BASED *VS* SINGLE INSTITUTION STUDIES

All single institution studies were retrospective and had relatively small numbers of patients with IPMNs. From their design, retrospective studies are limited by the fact that complete data can be missed if history of prior cancer is not documented. In addition, follow up data are limited if patients go elsewhere for diagnosis and/or treatment of additional neoplasms that occur after the treatment of their IPMN. Moreover, it is conceivable that the

patients seen at a referral center differ from and undergo different treatment when compared to the general population. At a referral center such as Mayo Clinic, the number of patients treated for IPMN is high when compared with non-referral centers. Given the heightened awareness of the referral center, this may have prompted colonoscopy or further surveillance studies with closer follow-up, thereby increasing the observed prevalence of extrapancreatic malignancies relative to population-based studies. Furthermore, the many of single-institution reports include only patients undergoing surgery. It is possible that this population has a different incidence of extrapancreatic malignancies than all patients with IPMNs.

Population-based studies also have inherent limitations. The correct classification of IPMN relative to other cystic pancreatic neoplasms was unclear until 1996 when the World Health Organization defined clear criteria for its diagnosis. As such, many IPMNs may have been misclassified as pancreatic adenocarcinomas or other cystic neoplasms in population-based studies. The U.S. population-based[7] study included patients from 1983-1991 only in order to follow all patients for ten years to determine the incidence of extrapancreatic malignancies after the diagnosis of IPMN and it is possible that many IPMNs are misclassified. In addition, this study included only invasive IPMNs since benign IPMNs (adenoma, borderline, or carcinoma-in-situ) are not registered in the SEER database. As such, this study could not evaluate the incidence in of extrapancreatic malignancies in benign IPMNs.

Regardless of their observed differences, all studies reached the same conclusion: there is an increased incidence of secondary malignancies in patients with IPMN when compared to the general population. This finding has significant implications in the management of patients with IPMNs.

CLINICAL IMPLICATIONS

The prognosis for patients with benign IPMNs is significantly better than for patients with invasive IPMNs, with 5-year survival rates of 60%-77% compared to 30%-50%[1,2]. As IPMNs (especially non-invasive) have a relatively favorable prognosis, associated extrapancreatic malignancies have potential prognostic significance. In patients who develop secondary malignancies, approximately 2% to 15% die from them[4,5,11,12].

Based on the literature, we recommend that a detailed personal and family history of previous cancers should be obtained when a patient presents with an IPMN. Given the increased risk of associated colonic neoplasms (either pre-malignant polyps or malignancy), a colonoscopy should be performed preoperatively if there is no history of colonoscopy in the ten years prior to diagnosis of IPMN. For patients in Asian countries or for those with history of upper gastrointestinal symptoms suggestive of gastric disease, an EGD should be obtained as part of the preoperative work-up. In addition, routine screening tests such as mammography for breast cancer, prostate specific antigen for prostate cancer, and digital rectal exam for prostate cancer should be up to date.

Data collected after the diagnosis of IPMN is made and therapy instituted are insufficient to develop systematic guidelines for surveillance for secondary malignancies in these patients. Because of the higher incidence of colonic neoplasia in patients with IPMNs, we recommend preoperative colonoscopy as described above. Based on the results of the preoperative colonoscopy, the current guidelines for colon cancer screening in patients with average risk should be followed. In patients older than 50 years, with a negative screening colonoscopy the guidelines for subsequent follow-up include: (1) fecal occult blood test or fecal immunochemical test every year, or (2) flexible sigmoidoscopy or multidetector computed tomographic colonography or double contrast barium enema every 5 years, or (3) rigid colonoscopy every 10 years after the age of 50 years if initial colonoscopy is negative[16]. There are no data regarding changes in the interval of routine screening tests for other malignancies such as breast and prostate cancer and screening for these malignancies should follow current national guidelines for the general population. Women should be screened for breast cancer with yearly clinical breast exam and mammograms after the age of 40 years. Men should undergo annual or biennial prostate specific antigen levels and digital rectal exam after the age of 50 years as recommended by the American Cancer Society.

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TOPIC HIGHLIGHT

Natural history of intraductal papillary mucinous neoplasia: How much do we really know?

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Abstract

Information on the natural history of intraductal papillary mucinous neoplasia (IPMN) is currently inadequate due to a lack of carefully orchestrated long-term follow-up on a large cohort of patients with asymptomatic disease. Based on the available data, one can draw the conclusions that main duct IPMN is commonly associated with malignancy and an aggressive operative stance should be taken with resection being offered to most patients who are suitable operative candidates. In contrast, the majority of branch type IPMN with a diameter of less than 3 cm can be safely followed with routine surveillance imaging provided they lack the high-risk covariates of age, symptomatology, nodularity or wall thickness.

Key words: Intraductal papillary mucinous neoplasia; Cystic pancreatic neoplasm; Pancreas

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Natural history is defined as the "study of the natural development of a disease over a period of time"[1]. While this task for intraductal papillary mucinous neoplasm (IPMN) of the pancreas may seem straightforward, the recent recognition of IPMN as a distinct pathological entity coupled with its histopathological complexity makes this assignment exceedingly difficult. The initial description of IPMN was published in 1982[2]. However, it was not until 1996 (further clarified in 2000) that the World Health Organization formally differentiated it from other mucin-producing cystic lesions of the pancreas through a uniform classification scheme[3,4]. With this consensus nomenclature came the realization that IPMN consists of a spectrum of neoplasms (subtypes include: gastric, intestinal, pancreatobiliary and oncocytic) which show both morphological and immunohistochemical variation[5]. It is currently unknown whether these four subtypes represent distinct pathological entities (with different biological potentials) or simply histological variations along a single progressive neoplastic lineage[6]. Confounding these distinctions is the ambiguity over the exact sequence of events and the precise time frame of histopathological lesion progression from noninvasive (adenoma, borderline tumor, carcinoma-in-situ) to invasive adenocarcinoma. Even with recent data supporting the concept of clonal progression in IPMN[7], evidence substantiating a stepwise and orderly evolution by way of the adenoma to dysplasia

to carcinoma sequence remains circumstantial at best[8-16]. In fact, while genetic evidence for the progression of pancreatic ductal adenocarcinoma is believed to be orderly and sequential (adenoma-carcinoma sequence), alternative theories of tumor development and progression do exist[17,18]. These differences may be explained by the recognition that not all IPMNs possess an equal potential for malignancy[19,20]. While there is broad consensus that the overall prognosis of patients with IPMN depends on the presence of invasive carcinoma, two distinct types of cancer (invasive ductal adenocarcinoma or invasive colloid carcinoma) associated with IPMN, each exhibit vastly different biological behaviors[6]. The five year survival rate in resected patients with IPMN was found to be significantly shorter ($P < 0.01$) in patients with invasive ductal adenocarcinoma (19%) than in patients with invasive colloid carcinoma (62%)[8]. These observations had been previously established by an independent group showing remarkably consistent findings of a five year survival rate of 12% for resected IPMN with invasive ductal adenocarcinoma *vs* a 57% five year survival for patients with colloid carcinoma[6,10]. These authors also found that colloid carcinoma was a favorable prognostic factor independent of patient age, tumor diameter or disease stage. Lastly, debate around the concepts of a local field defect versus disease multicentricity further clouds our understanding of the exact biology of these lesions[13,14,21-26].

As an epidemiological exercise, the ideal study to define natural history (prospective, longitudinal) would consist of a disease-free cohort undergoing continuous surveillance until they develop stage 1 disease (asymptomatic)[27]. In this idealized world, screening tests to detect disease have a sensitivity and specificity of 1.0. This cohort is then followed with periodic surveillance but without treatment until they develop stage 2 disease (symptomatic). Unfortunately, the majority of published literature on IPMN is either cohort or case-controlled studies that contain patients who have been treated (partial pancreatectomy). The overall level of evidence is poor[21]. It has been estimated, based on autopsy findings that up to 50% of all cadavers possess cystic pancreatic lesions[28]. This, coupled with the ubiquitous use of high resolution cross-sectional imaging, implies that identification of occult IPMN lesions seems likely to increase[29]. The paradox is that without properly constructed prospective observational trials at a time when the identification of IPMNs is becoming endemic, our understanding of its natural history is based solely on the extrapolation of indirect observations.

Given the limitations discussed above, a body of developing literature specifically devoted to IPMN was used as the foundation for this review. Based on these data, the natural history of IPMN lesions can be divided into two morphological subtypes: IPMN arising from the branch pancreatic ducts and IPMN arising from the main pancreatic duct. Main-duct IPMN involves and produces dilation of the duct of Wirsung. These lesions are associated with malignancy and invasive carcinoma in 43% to 70% of reported cases[21,30]. In contrast, branch-duct type IPMN lesions originate from side duct branches, do not involve the main pancreatic duct and are associated with invasive malignancy in only 15% to 25% of reported cases[13,14,31-36]. Despite the strong association between main duct IPMN and invasive adenocarcinoma, this connection does not prove causality or support any specific theory of carcinogenesis. Nevertheless, because of this strong association with malignancy, clinical exigency has resulted in consensus groups recommending operative excision of all main duct IPMNs[21,30]. These recommendations were broadened to include all "good-risk" patients with mixed-type IPMN (hybrid lesions involving both branch and main pancreatic duct)[30]. On a purely scientific note, the consequence of these proposals for aggressive resection will undoubtedly alter the landscape such that the "true" natural history of main duct IPMN may remain unknown.

In contrast to main duct IPMN, branch duct variants have significantly more published literature from which to make indirect inferences regarding their natural history. Approximately 90% of all lesions presumed to be IPMN (lacking definitive pathological analysis) which have undergone a period of surveillance without treatment have been branch duct variants[21]. Due to this wealth of surveillance data, a greater number of covariates have been identified in branch duct type IPMN that are associated with malignancy when compared to main duct IPMN. Tumor factors such as the size of a branch duct lesion (> 3 cm in cross-sectional diameter)[8,30,32,37-39], radiological characteristics (wall thickness or mural nodules)[37,40-43] or the presence of symptoms (jaundice, steatorrhea, new onset diabetes)[15,40,44] have all correlated with a higher incidence of associated invasive carcinoma. While lesions greater than 3 cm and the presence of mural nodules are associated with concurrent malignancy rates in resected patients of up to 82%, there is continued debate as to the utility of this measure to reliably predict tumor behavior[40,42,45]. In those series where invasive malignancy in branch duct IPMNs were not correlated with size, all had a high percentage of symptomatic patients, a known confounding variable, in their cohort[40,42,45]. Alternatively, the invasive malignancies identified in these patients might be synchronous malignancy at a site distant from the IPMN[46]. Broadly, it appears that the incidence of malignancy increases proportionately to the number of patients in the series with symptoms[8,13,38,39]. In point of fact, there are no known biological systems with sharp size "cutoffs". In this context, 3 cm likely constitutes an arbitrary threshold within a large continuum. Given these data, the natural history of branch duct IPMN is more aggressive in patients who present with symptoms, display mural nodules and/or solid components on imaging or possess lesions greater than 3 cm in cross-sectional diameter.

Patient age at the time of diagnosis represents another covariate in the natural history of IPMN. Resected patients with malignant IPMN are older than resected patients with benign IPMN[8,13-15]. On average, patients with malignant (invasive) IPMN are approximately 5 years older than pa-

tients with benign (adenoma or borderline) IPMN[8,14,15]. Of interest in this observation is the finding of an increased incidence of dysplastic changes in the lesions of older patients with IPMN[13]. Both observations lend weak indirect support to the theory of sequential genetic alterations consistent with clonal progression[7]. While age at the time of diagnosis is indirect evidence, non-operative surveillance of IPMN is the gold standard for defining natural history. The cumulative published experience of surveilling 450 patients with presumed branch duct IPMN using serial imaging and clinical examination indicates that very few asymptomatic, small (< 3 cm), branch duct lesions either enlarge (6% to 12%) or progress to invasive malignancy[16,19,21,35,36,39,47-51]. In these observations, the frequent lack of a firm histopathological tissue diagnosis also obscures the generalizability of these data. In addition, all have relatively short mean follow-up periods (maximum 40 mo) further complicating the interpretation of a neoplasm with a known indolent course. Following operation, the risk of recurrence in either the remnant pancreas or distant sites is high (up to 65%) in patients with invasive IPMN[13,14,21-23]. This rate is substantially lower (< 8%) in patients with noninvasive IPMN (adenoma, dysplasia, carcinoma in situ)[13,14,21-23].

In summary, the current literature regarding the natural history of IPMN is limited by selection bias (mostly resected patients), unclear definitions, varying inclusion criteria, heterogeneous patient groups, small nonoperative surveillance cohorts and relatively short follow-up periods[52,53]. Although these issues challenge our ability to accurately define the natural history of IPMN, it is clear that main duct IPMN at the time of its diagnosis commonly coexists with malignancy. These lesions should be resected when identified in patients who are suitable operative candidates since their risk of occult malignancy far outweighs their operative risk, even for pancreaticoduodenectomy. The clinical decision making for branch duct IPMN is more complex. To fully evaluate risk/benefit ratios in these patients, one must consider patient age, symptoms, lesion size, radiological findings, type of operation and the ability of a patient to potentially engage in a lengthy surveillance program. Most branch duct IPMN are currently being identified with a diameter of less than 3 cm, a size which, given the lack of other high risk covariates (age, symptoms, nodularity, thick wall), can be safely surveilled[54]. Only with the combination of long periods of observation and direct evidence of true malignant transformation (or lack thereof) will we be able to better define the natural history of IPMN.

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Meetings

Events Calendar 2010

January 15-16, 2010
AGA Clinical Congress of Gastroenterology and Hepatology
The Venetian And Palazzo, 3355 Las Vegas Blvd South, Las Vegas, United States
http://www.gilearn.org/clinical-congress

January 27-31, 2010
Alpine Liver & Pancreatic Surgery Meeting
Carlo Magno Zeledria Hotel, Madonna di Campiglio, Italy
http://www.alpshpbmeeting.soton.ac.uk

February 25, 2010
Multidisciplinary management of acute pancreatitis symptoms
The Royal Society of Medicine, 1 Wimpole Street, London, United Kingdom
http://www.rsm.ac.uk/academ/pancreatitis10.php

March 4-7, 2010
2010 Annual Meeting of the Society of Surgical Oncology
Renaissance® St. Louis Grand Hotel, 800 Washington Avenue, St. Louis, Missouri, United States
http://www.surgonc.org/

March 25-28, 2010
20th Conference of the Asian Pacific Association for the Study of the Liver
Beijing, China
http://www.apasl2010beijing.org/en/index.aspx

April 14-18, 2010
The International Liver Congress™ 2010
Vienna, Austria

May 1-5, 2010
2010 American Transplant Congress
San Diego Convention Center, 111 West Harbor Drive, San Diego, United States
http://www.atcmeeting.org/2010

May 1-5, 2010
Digestive Disease Week 2010
Ernest N Morial Convention Center, 900 Convention Center Blvd, New Orleans, United States
http://www.ddw.org/

May 15-19, 2010
Annual Meeting of the American Society of Colon and Rectal Surgeons
Hilton Minneapolis Hotel & Convention Center, Minneapolis, Minnesota, United States
http://www.fascrs.org/

September 16-18, 2010
Prague Hepatology Meeting 2010
Prague, Czech Republic
http://www.congressprague.cz/en/kongresy/phm2010.html

September 23-25, 2010
2010 Gastrointestinal Oncology Conference
The Sheraton Philadelphia City Center, Philadelphia, United States
http://www.isgio.org/isgio2010/program.htm

October 20-23, 2010
Australian Gastroenterology Week
Melbourne, Australia
http://www.gesa.org.au/agw.cfm

November 13-14, 2010
Case-Based Approach to the Management of Inflammatory Bowel Disease
San Francisco, United States

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5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

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16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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