

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.

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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 than 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 100000 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 26/100000 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....

THE 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 mimics 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 pathologi-

cal 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 Schlick 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 Main-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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