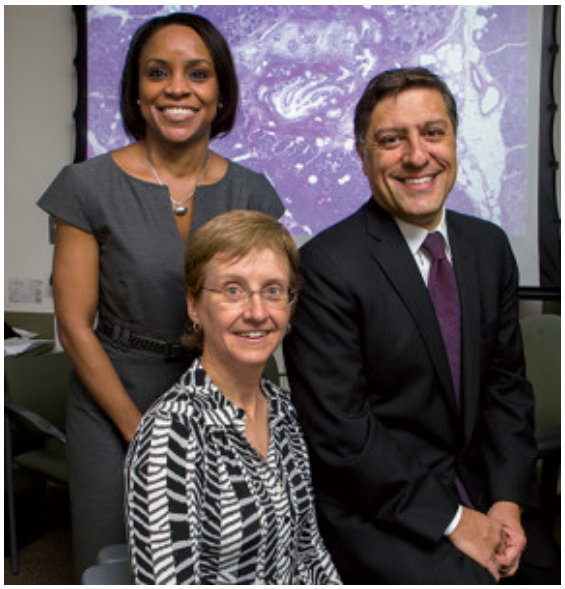
New guideline spells out IPMN essentials

Karen Titus

June 2015—It was a call he dreaded making.

It was the late 1990s. Volkan Adsay, MD, was following up on a former patient who had been diagnosed eight years earlier with pancreatic cancer, one related to an intraductal papillary mucinous neoplasm. The patient's medical record noted that despite chemotherapy, the prognosis was grim.



Lead author Dr. Volkan Adsay (right), with coauthors and Emory pathologists Alyssa Krasinskas, MD (front), and Michelle Reid, MD. The new guideline fills a gap in IPMN pathologic evaluation and reporting, says Dr. Adsay. "A lot of pathologists are being exposed to this entity."

"Everybody was expecting him to be dead," recalls Dr. Adsay, professor and vice chair and director of anatomic pathology at Emory University. "So I was preparing a very apologetic phone call: *I'm sorry to be bothering you, but your father, or your spouse, had this tumor, and we wanted to find out when he died."*

Such was the nature of IPMNs not so long ago. "These tumors were called ordinary pancreas cancers just 20, 25 years ago," Dr. Adsay says. "And many patients were sent home to die."

When Dr. Adsay placed the call, he was in for a shock. "The patient himself picked up the phone," he recalls, the surprise—and delight —still evident in his voice nearly two decades later.

As it turns out, IPMNs are more complicated than first thought, and patients once consigned to a certain mortality, can—as Dr. Adsay discovered—reappear, so to speak, like a character in a Thomas Hardy novel.

Now, no longer willing to rely on fate and muddled data, experts on IPMNs have written a new guideline on their pathologic evaluation and reporting, which was published online March 13 in the *Annals of Surgery* (Adsay V, et al. 2015).

The time was ripe. "The tumor type is relatively new and not as well known," says Dr. Adsay. "There's been a big

learning curve for both pathologists and clinicians. And it's still a challenging tumor type, both for management and diagnostic purposes."

Hence the impulse behind a 2013 meeting by the Verona (Italy) Pancreas Group, which brought together a multidisciplinary group of 60 to 70 people (per Dr. Adsay's estimate), including those from pathology, surgery, and gastroenterology. The main parameters of the guideline came primarily from discussions at the Verona meeting, says Dr. Adsay. But after that he sought input from other pathologists via questionnaires. He compiled that information and ran it by the original committee and organizers of the Verona meeting. All of which is to say, "There were many steps to getting input" before the final manuscript emerged.

The guideline fills an obvious gap. Though they were first recognized in 1982, IPMNs hardly took medicine by storm.

No one quite knew what to call them, for starters. Prior to the use of the term "intraductal papillary mucinous neoplasms" in 1994, their identities were never fully settled, as if they were passing repeatedly through Ellis Island, their names changing each time: duct-ectatic mucinous cystic neoplasms, mucin-producing tumors, intraductal papillary neoplasms, papillary adenocarcinomas, and villous adenomas, among others.

Nor did it seem to matter, at first, what they were called. "They were thought to be relatively rare tumors. Back then it was extremely uncommon to find them, and we didn't know how to interpret the findings," says Dr. Adsay.

Dr. Anne Marie Lennon (above), who oversees the Multidisciplinary Pancreatic Cyst Clinic at Johns Hopkins, says colleagues such as Dr. Ralph Hruban (center) and Dr. Christopher Wolfgang (left) "bring huge depths of knowledge" to patient management discussions each week. "We all learn from each other."

All that has changed. "Now we're discovering them in high frequency," he says. The rise is due in large part to more widespread use of MRIs and other imaging modalities. As Dr. Adsay points out, endoscopic ultrasound didn't exist when IPMNs first emerged, and even core needle biopsy of the organ was uncommon. ("Everybody was scared to poke the pancreas," he says, "because it could lead to pancreatitis.") The sensitivity of these modalities has also improved.

Most of these cystic lesions appear incidentally during workup for other diseases, which creates a major management question, says Dr. Adsay. Should they be resected? Or is it reasonable to follow them closely?

The literature has provided limited guidance, unfortunately. From one study to the next, a slackness crept into the

IPMN lexicon. More recently, in his post-Verona, pre-guideline survey of pathologists, Dr. Adsay says he found a fair amount of variation among how pathologists—including experts—reported IPMNs.

One stark example: Not everyone agreed on what the word "malignant" meant.
Some groups reported noninvasive cancers as being malignant or included high-grade dysplasia in that category, others applied the word to invasive cancers, and yet others reserved it for only those tumors that involved recurring metastases. "Those years of research are hard to interpret because of the loose terminology," says Christopher Wolfgang, MD, PhD, chief of hepatobiliary and pancreatic surgery and the Paul K. Neumann professor of pancreatic cancer research, the Sol Goldman Pancreatic Cancer Research Center, Johns Hopkins University School of Medicine. Some groups also reported that some patients with malignant IPMNs did just fine (which helps explain Dr. Adsay's surprising phone call), while others found that malignant IPMNs did indeed lead to mortality.

The new guideline tries to impose order on this and other chaos. It couldn't come at a better moment. "There's a virtual epidemic of patients being diagnosed with IPMNs," says another guideline author, Ralph Hruban, MD, professor of pathology and director of the Sol Goldman Pancreatic Cancer Research Center, Johns Hopkins. "And there's controversy clinically as to how they should be managed. This is an exciting time for pathologists who are involved in the care of patients with intraductal papillary mucinous neoplasms."

That's quite a few pathologists. Ten, or even five, years ago, IPMNs would have been termed a problem for specialists alone, Dr. Adsay says. Now, "A lot of pathologists are being exposed to this entity."

That means surgeons are, too. Although Dr. Wolfgang (who is a guideline author) is no stranger to IPMNs, he and his colleagues still struggle at times to unravel their meaning. "The most challenging thing about the IPMN is that the vast majority of these are premalignant lesions, and we don't know how many will progress to cancer."

Here's how the guideline, with its obbligato of precision (not to mention a sample synoptic report), might help.

Tumor size

As Dr. Adsay learned when he queried colleagues both in Verona and afterward, there's plenty of variation in how pathologists report IPMN tumor size.

The invasive component—the true cancerous component—needs to be reported as a separate item, says Dr. Adsay. But this is not always done. Instead, he says, pathologists were reporting both cancerous and noncancerous components—the entire tumor—together, which clouded assessment of individual patients as well as overall understanding of their biology.

"These tumors can be large—six, seven centimeters—but still be preinvasive," Dr. Adsay says. But they might have a small invasive focus. "That needs to be acknowledged separately." Is the whole tumor cancer, or just a small percentage? Failure to distinguish the two components on pathology reports "was probably the biggest problem we encountered," he says.

That leads to a discussion of size. "It's not easy," Dr. Adsay concedes, noting that a similar difficulty occurs with breast cancer, especially if the invasive cancer is multifocal. "Do you measure the largest focus? Do you combine the sizes?" In breast, he notes, the decision has been made to use the largest focus for staging. "The other foci are kind of ignored." But, he notes, the discussion continues, since there are studies showing that the size in aggregate may correlate better with the cancer's behavior.

For measuring overall IPMN tumor size, the guideline says that while size becomes less significant in resected specimens, "Regardless, every attempt should be made to accurately determine the size of the lesion in the pathology report."

Noting that some IPMNs have thin-walled cysts prone to rupturing, the guideline advises pathologists to correlate size with imaging findings, and to document the mode of measurement: "For example, 'Overall size of IPMN: 3 cm, as measured clinically (cyst ruptured during processing).'"

Measuring size of the invasive carcinoma is just as challenging and even more important. If the invasive carcinoma is unifocal, pathologists should measure the largest diameter of the invasive focus, according to the guideline. For multifocal tumors, pathologists should report both the diameter of the largest one and the overall estimated size of all foci in aggregate.

Persuading pathologists to report the two components separately is, says Dr. Adsay, "I hope, the most important accomplishment of this guideline."

Terminology

As mentioned, the guideline wrestles the word "malignant" to the mat.

In fact, it recommends eliminating the term "malignant IPMN" and instead clarifying whether the IPMN is invasive.

Then there's the term "minimally invasive." Like "malignant," the guideline would like to move this term to pathology's no-fly list.

Dr. Basturk

"That was another aspect that was extremely confusing in the literature," says Dr. Adsay. It's not unusual, he says, for him to see a surgical pathology report call a tumor "minimally invasive," and then, when he reviewed it, to discover it had a 1 1/2- to 2-cm invasion. "Or it will be called minimally invasive, and I'll review the case in consultation, and it will have indefinite invasion, maybe a fraction of a millimeter. Or nothing. Which makes a big difference in terms of prognosis." As the guideline notes, the most important determinant of outcome is the presence or absence of an invasive carcinoma.

A look at the literature shows that the term "minimally invasive" has been scattered rather indiscriminately through various studies, like so many dandelions in a lawn. That makes data hard to compare, says Olca Basturk, MD, another guideline author. Some call these lesions indolent. "Others are saying, 'Oh, they're not that innocent—a lot of people are dying from minimally invasive carcinomas,'" says Dr. Basturk, assistant professor, Department of Pathology, Memorial Sloan Kettering Cancer Center. "Everyone's 'minimal' is different."

The guideline advocates avoiding what Dr. Adsay calls "this noncommittal and blurry name" and to give a more specific measurement instead.

"Indeterminate" should also be used sparingly, according to the guideline. The word reflects the very real challenge of IPMNs—that they are complex, and that it can be difficult to determine the invasive and noninvasive components. Even experts find this difficult, so it's not surprising that those in general practice find them tough to distinguish, too, says Dr. Adsay. (And that's why, when asked, Dr. Adsay says the guideline is aimed at both experts and nonexperts. Everyone, he says, struggles with IPMNs.)

"So we created a category of 'indeterminate' or 'suspicious for invasion' for cases that we cannot determine whether we are dealing with a small invasive focus or not," says Dr. Adsay. He compares them to gray zone lesions in the breast literature, and urges pathologists to get second and even third opinions as needed. This isn't a junk drawer for IPMNs, he cautions. "We emphasize this in the manuscript: This should be used very stringently." Every attempt should first be made to determine if it's invasive. "We don't want this term to be overused."
But there is a need for the term, Dr. Adsay says. Before this, surgeons and clinicians found it hard to understand when pathologists told them they weren't sure of the tumor's invasive status. "Indeterminate" wasn't applied to

IPMNs, even though “there are cases that are impossible to determine.”

One of the strengths of the guideline, says Dr. Hruban, is that it gives pathologists a strong pathologic basis for evaluating IPMNs: whether the IPMN involves the main duct or a branch duct; size/extent of dilatation of the main duct; presence of solid nodules. “All those are features that our clinical colleagues use to determine whether or not an IPMN should be resected.”

The guideline’s emphasis on measurement and separation will influence future research as well as patient care, says Anne Marie Lennon, MB, PhD, assistant professor of medicine and surgery at Johns Hopkins, where she is also director of the Multidisciplinary Pancreatic Cyst Clinic. “There are now multiple reports of pancreatic ductal carcinoma arising separate from the IPMN.” Having pathologists provide more precise classification will help clinicians identify true risk. “We don’t have great data on this,” she says.

The other critical aspect of the guideline, as far as Dr. Hruban is concerned, is the guidance it provides in distinguishing between an IPMN that has high-grade dysplasia and one that has an associated invasive cancer. “That’s by far the most important pathologic distinction,” he says, one that in the past has been blurred by use of terms such as “cystadenocarcinoma.” As an example of the importance of using the *mot juste*, Dr. Hruban offers this comparison: “It’s as if one looked at our current hospital charts for the term ‘Bright’s disease.’ If you don’t find it, you wouldn’t say, ‘Well, nephritis isn’t a clinical problem anymore.’”

IPMNs present microscopic as well as nomenclature challenges, Dr. Hruban continues. As the name implies, IPMNs involve the duct system. “So the neoplastic cells can extend into smaller and smaller pancreatic ducts, and in cross-section the small-duct involvement can mimic an invasive cancer,” he says.

Yet another challenging area is that with many IPMNs, the mucin accumulates in the pancreatic duct, which risks rupture. “One can observe mucin extruded into the stroma of the pancreas,” says Dr. Hruban, “and this mucin extrusion can be very difficult to distinguish from true invasion of the pancreas.” Neoplastic glands floating in the stromal mucin are a feature of invasive cancer, he says, as are neoplastic cells when found in a place they don’t belong, such as in a perineural space. As the guideline notes, acellular stromal mucin, while not invasive carcinoma, can be hard to distinguish from true invasive colloid carcinoma. In such cases, the term “indeterminate for invasion” may be useful, though it should be accompanied with a comment giving the estimated size of a suspect focus.

Tumor biology

The nature of the tumor can create misunderstandings among clinicians, Dr. Adsay says. “They’re kind of adenomatous lesions that can either develop into cancer or harbor cancer.” Not everyone appreciates that basic fact, he says; moreover, even though thinking has evolved, for too long patients with IPMNs were thought to require large resections of the pancreas.

Physicians also struggle to understand the two invasive cancer types that arise from IPMNs. The colloid and non-colloid types have different biologies, says Dr. Adsay, a fact that not even pathologists fully appreciate.

As the guideline explains, about half of the invasive carcinomas that arise from an IPMN are ordinary tubular, or ductal, adenocarcinomas and appear to be aggressive, marked by infiltrating small to medium tubular units separated by abundant stroma.

The other half are colloid carcinomas, and patients with these types of invasive carcinoma have a much better prognosis—more than half of these patients live at least five years. These are relatively rare in the pancreas, and they can be quite small, says Dr. Basturk. “So people may not recognize them”—hence the emphasis in the guideline on distinguishing between the two types. The ductal type is more common and more familiar.

Frozen sections

The discussion on frozen sections made the multidisciplinary nature of the guideline abundantly clear. Some

surgeons advocated for doing frozen section on the primary tumor. Long discussions ensued, and pathologists largely succeeded in convincing their clinical colleagues that frozen sections needed to be performed selectively.

The guideline acknowledges that dialogue, saying that if routine frozen section of the primary tumor is performed, everyone needs to be aware of its limitations: 1) focal high-grade dysplasia and invasive carcinoma—the main targets of frozen section—cannot be excluded in this setting; 2) even when present, a high-grade dysplasia and/or carcinoma focus is difficult to interpret histologically; 3) freezing tissue can alter the specimen and affect final diagnosis.

“I would have personally written the guideline even stronger,” says Dr. Adsay. “But some of the surgeons thought there were occasional cases where they might want that information, so we had to tone down the guideline a bit.” But his view is unequivocal: Heavy reliance on frozen section would put pathologists in a challenging position “without any good justification,” he says, since it is prone to mistakes in the IPMN setting.

Particularly at centers that handle fewer IPMN cases, says Dr. Basturk, surgeons might ask for a frozen section out of curiosity. “This is problematic, because to evaluate an IPMN you need optimal sections—and frozen section, we all know, is suboptimal.” If surgeons do request unnecessary frozen sections, she says, pathologists can refer them to the new guideline, which has the added heft of including expert surgeons as authors.

Frozen section is justifiable for assessing margin status, as the guideline notes, although the above concerns still hold. If there are foci of invasive cancer in the margin, a total pancreatectomy may be justifiable. But using a frozen section to identify lesser lesions, low-grade dysplasia, and the like is not important, and not sufficient reason to do a frozen section. And doing a frozen section on primary tumor to determine grade doesn’t make sense, says Dr. Adsay, since it won’t alter surgical management.

Sampling

Given the adenomatous nature of these tumors, “Before you can call it noninvasive, you have to examine the entire lesion,” says Dr. Adsay.

The guideline doesn’t mince words, saying that an IPMN-associated invasive carcinoma can be definitely excluded only with thorough evaluation of the entire lesion and the uninvolved pancreas, which often shows peritumoral abnormalities and may contain subtle invasive carcinomas.

When she goes to meetings or gives courses, says Dr. Basturk, “That’s one of the most commonly asked questions—people ask if it’s really necessary. They’re questioning it, because it’s kind of a new concept.” Her response: If a clear-cut invasive component is found during a gross examination, submitting the entire pancreas isn’t necessary. But in most of the cases, no such component will be evident. “So for those cases, you have to submit at least the entire IPMN. We tell them, at our institution, we’ll even submit the entire pancreas.” IPMNs can be associated with invasive carcinomas that are totally separate from the IPMN, she warns. “To rule that out, you should at least examine the rest of the pancreas very carefully and try to submit as many sections as possible.”

She’s also asked about cost. Though IPMNs are far more common than previously thought, most hospitals will still see fewer than one a month, she estimates. “So it doesn’t increase the cost that much.” Memorial Sloan Kettering sees, on average, one to two a week.

Dr. Basturk likes to use the analogy to breast cancer. “With breast, we submit the entire lesion,” she says. That tends to convince her colleagues. “Every hospital sees a lot of breast specimens, and we all know we have to extensively—if not completely—sample those specimens.”
“It’s important,” she adds. “The invasive component of IPMNs can be very small, but the consequences are big.”

Invasive foci in IPMNs can be very focal, agrees Dr. Hruban. “It’s therefore important that these are examined extensively, if not completely, histologically,” he says. This can result in a large number of sections and blocks. “Some pathologists are reluctant to do this. But because invasion can be focal, it’s critical.”

This has been a hard-won lesson. Many early studies showed, surprisingly, that even noninvasive cases could behave aggressively, like a sly duke in a Shakespeare play. Of course, that didn't make sense. "We realized that this was because they undersampled, and the cancer's foci were missed," says Dr. Adsay.

Consensus within the pathology community was fairly widespread as the guideline evolved, Dr. Adsay reports. There were, of course, spirited discussions that occurred with other specialties. But the final guideline represents a wide consensus among all groups, he says.

That's not always the case with so-called consensus guidelines, he adds; it's a word the medical profession has learned to view with some skepticism. "Usually there are drivers, and they push their opinions. Sometimes it's a compromise rather than a true consensus. But I feel fairly confident that this manuscript represents a pretty good consensus among most of the experts. It's unusual."

Dr. Wolfgang agrees. The Verona attendees all had their own terms and perspectives at the outset, he says, "though, in the end, we were all talking about the same thing."

At Johns Hopkins, similar multidisciplinary conversations have been taking place for some five years at the pancreatic cyst clinic. Says Dr. Hruban, "As a pathologist, it's been wonderfully rewarding, because it helps me understand what the clinical questions are, and to include in my report what the clinicians want to know."

Dr. Wolfgang makes it clear what surgeons want. In patients who have undergone a resection, what's the status of the tumor—is it an IPMN or some other type of cystic lesion? If it is an IPMN, what is the degree of dysplasia—low-, intermediate-, or high-grade? Is there an invasive focus, and, if so, has it arisen within the IPMN, or is it a separate concomitant ductal adenocarcinoma? Finally, what's the margin status, in particular, the pancreatic neck margin, the uncinate margin, and the bile duct margin?

The two most important questions Dr. Hruban says he hears from clinical colleagues are:

- In this patient with a cyst, should the patient undergo surgical resection? Many, though not all, can be safely observed, a la the active surveillance of prostate cancer.
- If the patient does need surgery, how much of the pancreas needs to be resected? The multifocal nature of IPMNs makes this a challenging question. "If you have one IPMN in the head of your pancreas, you're more likely than the general population to have a second IPMN in the tail of your pancreas," Dr. Hruban says.

Johns Hopkins has a similar clinic for pancreatic cancer as well; the two overlap considerably. "We say they're two different teams," says Dr. Wolfgang, "but it's really the same players on both." That adds to the continual, and clear, conversations between all disciplines. "I get almost immediate feedback and correlation from our pathologists," he says.

There's nothing especially astonishing about the clinic, says Dr. Lennon, apart from the vast experience of many attendees. "Every Monday evening, all of us sit down in the same room," she says. With every specialist present and every finding on the table, it's far easier to decide what to do. Established in 2010, the clinic has been "incredibly helpful," she says. In a study looking at its impact (Lennon AM, et al. *Ann Surg Oncol.* 2014;21:3668–3674), she and her colleagues found that after clinic review, the management category was altered in 68 (30 percent) of 225 patients. In 52 patients, management was increased, including 22 who were recommended for surgical resection. In the 16 patients whose management was decreased, 10 had their recommendation changed from surgery to surveillance.

There’s no reason other institutions can’t replicate the experience, she says. “It just requires people willing to meet up for 30 to 60 minutes every week to review things.”

This is not the end—not for the guideline, which, like any, will eventually be revised, nor for the topic. Dr. Basturk mentions a second consensus manuscript, submitted for publication, that will deal with the grading of preinvasive neoplasms, including IPMNs. And the exploration of IPMNs’ molecular makeup—and the subsequent development of related tests—is only at the early stage.

But for Dr. Adsay, the guideline must be a satisfying moment in the study of a tumor that has long interested him. “One of the ways I became acquainted with these tumors was, in my first faculty position, I pulled out all the pancreatic resections—every single one of them—and reviewed them from top to bottom, multiple times, to learn the organ and subtle changes and subtle differences of different tumor types,” he recalls. “And that’s how I came to recognize these things.” But even so, “They’re still difficult. It’s a difficult organ.”

Fortunately, some things have become easier over time, including for patients, as his aforementioned phone call suggests.

What happened when Dr. Adsay reconnected with the patient he’d thought would be dead? “It was a peculiar phone conversation, as you can imagine,” he says.

Dr. Adsay had done a two-year surgery residency, so he was well versed in working with patients and had prepared his words carefully. Instead, when the patient picked up the phone, “I was able to tell him how happy I was.” The patient reported feeling perfectly fine—no problems, no pancreatitis, and, of course, he was still alive.

“It was wonderful to hear,” says Dr. Adsay.
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