CLINICAL MANAGEMENT OF INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS OF THE PANCREAS

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In the 20 years that have elapsed since its initial description by Ohashi and coworkers, intraductal papillary mucinous neoplasm (IPMN) has become one of the most common diagnosis in the field of pancreatology. Its epidemiology, natural history and proper management remain in a state of flux, and therefore surgical treatment is not standarized.

In its classic form, which was formerly referred to as mucionous ductal ectasia, IPMN presents as a dilated pancreatic duct, full of mucus that extrudes through a bulging ampulla. Patients have recurrent episodes of pancreatitis-like pain, with or without hyperamylasemia, and not infrequently have steatorrhea, diabetes, and weight loss. Not surprisingly, this clinical picture has led to the diagnosis of chronic pancreatitis in many of these patients. In this form of IPMN, the tumor originates in the main pancreatic duct, more commonly in the cephalic portion, and from there spreads to the rest of the duct.

It is now well-recognized that IPMNs can also originate in the side branches of the pancreatic ductal system. These occur mostly in the uncinate process of the pancreas, but can be seen in the neck and distal pancreas as well. A large proportion of these patients are asymptomatic, and are detected by CT or ultrasound done for other reasons, but others present with abdominal pain or pancreatitis. It is unclear if this variant represents an entity that mostly remains localized or one that inevitably will spread into the main ductal system, but studies do show that the side-branch IPMNs have smaller tumors and a lesser likelihood of malignancy .

Both main and branch-duct IPMNs occur typically in the seventh and eighth decades of life. Initial reports suggested a strong male predominance, but more recent series indicate an equal distribution. In a recent experience with 140 patients, more than 25% of were asymptomatic, and the most common symptoms were abdominal pain (65%), weight loss (44%), acute pancreatitis (23%), jaundice (17%), diabetes (12%), and steatorrhea (6.5%).

Histopathologically, IPMNs encompass a spectrum of epithelial changes ranging from adenoma to invasive adenocarcinoma, with borderline tumors and carcinoma in situ in between. Like in mucinous cystic neoplasms, extensive sampling of the specimen is required to rule out cancer. In our experience, 42% of patients with main duct IPMN have invasive carcinoma and 18% have in situ tumors. Patients with malignant IPMN tend to have larger tumors, a larger proportion of solid component, and a higher incidence of jaundice or recent-onset diabetes. The average age of patients main-duct IPMN and malignant tumors is 6.4 years older than those with adenomas or borderline lesions. This

supports the current view that most if not all main duct IPMNs eventually become malignant.

The surgical management of main duct IPMNs is different than that of serous cystadenomas and mucinous cystic neoplasms. Whereas in the latter two from the preoperative studies the surgeon can accurately locate the tumor an accordingly plan a segmental pancreatic resection (either a Whipple, a distal, or a middle pancreatectomy), that is not always the case in IPMN. In IPMN preoperative studies will show a dilated pancreatic duct in the main duct variety, but not necessarily the intraductal mass, which is often small. Because of the overproduction of mucus, dilation can occur both proximally and distal to the tumor, making location problematic. This difficulty is compounded by the propensity of the tumor to spread microscopically along the duct.

At the Massachusetts General Hospital it is our policy to obtain a spiral CT and an ERCP or an MRCP in all patients with suspected IPMN. Furthermore, we often obtain endoscopic ultrasound to better define any intraductal mass, and to sample both the fluid and solid components. With this information, we plan the surgical intervention (be it a Whipple procedure, a distal, a total or a middle pancreatectomy, with or without splenic preservation), but are prepared to change this plan depending on the intraoperative findings. We have not found that intraoperative ultrasound adds much more to the preoperative imaging, but rely heavily on the frozen section diagnosis of the transection margin of the pancreas.   Since IPMN extends along the pancreatic duct and can do so without obvious macroscopic tumor, it is important to rule out presence of tumor in the margin so as not to leave tumor behind.   A denuded epithelium within the duct is not uncommon in this pathology, and de-epithelialization should not erroneously interpreted as a "negative" margin, since recurrence has ocurred often in this setting. We are also utilizing intraoperative pancreatoscopy to inspect the ductal system of the remaining pancreas. This can potentially identify "skip" lesions if they are macroscopic. The presence of these skip lesions has been proposed on the basis of recurrence of IPMT in the remaining pancreas in the setting of a truly negative transection margin .

Because of the potential to modify or extend the surgical resection plans at the time of surgery, it is important that the surgeon discuss and evaluate preoperatively the risks and consequences of a total pancreatectomy with the patient. This obviously needs to be individualized carefully. Whereas a total pancreatectomy may be appropriate in a young, fit patient who has an IPMN with carcinoma in the head of the pancreas that is extending into the body and tail, it may not be the right operation for an elderly or frail patient with an IPMN that is only an adenoma or borderline tumor, even if present at the transection margin. In our experience, 63% of patients have required a Whipple procedure (not infrequently extended to the left of the mesenteric vessels), 17% a distal pancreatectomy, and 19% a total pancreatectomy. In 29/140 cases, results of the frozen transection margin altered the surgical plan, underscoring the importance of this information transoperatively.

The survival of patients with IPMN, even when malignant and invasive, can be quite good . In our recent experience with follow-up of 137 resected patients, five-and ten-years disease-specific survival for 80 patients with adenoma, borderline tumors, or carcinoma in-situ was 100%, and the comparable statistics for the 57 patients with invasive carcinoma were 60% and 50%. 41% of patients with invasive cancer had positive lymph node metastases, and remarkably, their 5-year survival was 45%, which is

markedly better than that of the usual ductal pancreatic adenocarcinoma, wherein long-term survival of resected patients with positive lymph nodes is rare . If recurrence occurs in the remaining pancreas, a resection is warranted, since several series have shown that some of these patients are salvageable . This may indeed be one of the most curable forms of pancreatic cancer.

The management of branch duct type IPMN is different than that of the main-duct variant. Whereas in main duct IPMN, in appropriate surgical candidates (even if asymptomatic) we always recommend surgical resection, that is not the case in the branch duct form. Review of 7 recent series describing branch duct IPMNs show a frequency of malignancy between 6% and 40%, with a mean of 25%, and a frequency of invasive cancer ranging between 0% and 31%, with a mean of 15%. Furthermore, several studies from Japan have shown that size and morphology correlate with malignancy, and that tumors that are 3 cm or less and have no mural nodules do not have invasive cancer. With this criteria, there is at least one study that has followed patients radiologically (for a mean of 33 months), and found that the majority do not progress. Thus, the overall lower prevalence of malignancy in branch duct IPMNs and the reassurance from the above studies that the likelihood of invasive cancer is very low in small cysts, raises the possibility of management with careful observation in asymptomatic patients. Patients with branch duct IPMNs who are symptomatic should be treated with resection not only to alleviate the symptoms, but also because of a higher likelihood of malignancy. It is important to emphasize that the decision to treat should be individualized and based on patient preferences and willingness or unwillingness to undergo follow-up studies, as well as on the availability of safe pancreatic resection.

Recommended Reading

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