**Early Detection Tools for Pancreatic Cancer**

By Charlie Schmidt

Finding pancreatic cancer while it’s still curable with surgery remains one of oncology’s most frustrating challenges. A growing pancreatic tumor can take more than 15 years to metastasize, during which patients generally aren’t symptomatic. When they finally experience abdominal pain, weight loss, and other hallmarks of the disease, it’s usually too late: Pancreatic cancer almost always kills within 2 years of diagnosis.

But research funding for pancreatic cancer is up from $17.3 million in 1999 to $96.5 million today, according to the Pancreatic Cancer Action Network in Manhattan Beach, Calif. Meanwhile, researchers are making steady progress in early detection, focusing on blood biomarkers that might reveal the illness noninvasively and imaging tools that reveal potentially curable precursor lesions. Between them, imaging has made much bigger gains, according to Teri Brentnall, M.D., a gastroenterologist and professor at the University of Washington in Seattle. “The imaging world is on fire right now,” Brentnall said.

**Biomarkers and Imaging**

Brentnall and other researchers agree that noninvasive blood biomarkers could be ideal for pancreatic cancer screening. But so far, candidates with the sensitivity and specificity to accurately detect tumors haven’t emerged. In 2010, researchers led by David V. Gold, Ph.D., of the Garden State Cancer Center in Morris Plains, N.J., announced that a serum antibody called PAM4 could detect stage I pancreatic cancer in 62% of affected patients; the team reported similar results in a larger study last January at the Gastrointestinal Cancers Symposium in San Francisco. But they haven’t yet achieved a better detection rate. When Gold’s research team combined PAM4 with CA19-9, a biomarker used routinely to monitor pancreatic cancer progression, they detected more advanced illness in 85% of patients, but stage I detection remained at about the same level achieved with PAM4 alone. PAM4 and CA19-9 may be the best serum biomarkers for detecting pancreatic cancer today, but they miss many stage I patients. “And even stage I is too late for pancreatic cancer,” Gold said. “Most patients with stage I illness will die from it.”

However, computed tomography (CT) can now pick up precancerous pancreatic cysts measuring just 3–4 mm, according to Michael Goggins, M.D., a pathologist and professor with the Sol Goldman Pancreatic Research Center at Johns Hopkins Medical Institutions in Baltimore. CT’s radiation risks make it impractical for routine screening, so clinicians—researchers at Johns Hopkins and elsewhere rely on endoscopic ultrasound and a specialized tool called magnetic resonance cholangiopancreatography (MRCP) to look for precancerous lesions in high-risk individuals.

A study accepted for publication in *Gastroenterology* compared all three approaches. Conducted through the Cancer of the Pancreas Screening (CAPS 3) study, based out of five U.S. academic medical centers, including Johns Hopkins, the study showed that MRCP and endoscopic ultrasound could detect pancreatic abnormalities (mostly small pancreatic cysts) in 33.3% and 42.6% of asymptomatic high-risk patients, respectively. CT, however, detected abnormalities in just 11% of the patients. Endoscopic ultrasound could identify cystic lesions 93% of the time, compared with 81% for MRCP and 27% for CT. According to Goggins, CT is better for cancer staging, whereas ultrasound and MRCP are better for locating tiny cysts. Moreover, unlike other approaches, endoscopic ultrasound can supply samples for analysis. Goggins and his colleagues at Johns Hopkins recently began looking for biomarkers in pancreatic fluid that might reveal high-grade pancreatic intraepithelial neoplasias (PanINs). PanINs can progress to cancer, but they’re also microscopic, so traditional imaging tools can’t detect them.

**Looking for High-Risk PanINs**

But Kimberly Kelly, Ph.D., an assistant professor at the University of Virginia in Charlottesville, has developed a way to detect PanINs and smaller tumors. Clinical trials later this year will test her method. According to her research, PanIN-3, which tends to become cancer, often expresses a cell-surface protein called plectin that Kelly targets with a specific peptide. That peptide can be linked to a radioactive tracer, indium-111, that functions as a contrast agent. After infusion into the bloodstream, that complex travels to the pancreas and binds to plectin proteins on the PanIN-3 and cancer cell surface. Kelly can “see” these entities with an imaging tool known as single-photon emission computed tomography (SPECT). That the imaging complex targets transformed cells is important, Kelly said, because many people have early pancreatic lesions, most of which will never become tumors. “The SPECT test is like an in vivo biopsy,” Kelly said.

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Teri Brentnall, M.D.
said. “You want that because the pancreas doesn’t like to be manipulated—it’s easy to damage the organ and incite pancreatitis, so you want to be sure the lesions are dangerous before you go in and sample them directly.”

Who’s at Risk?
Kelly emphasized that like other screening tests for pancreatic cancer, the SPECT test would be offered to high-risk individuals. What constitutes high risk for pancreatic cancer is still evolving, however. The CAPS studies have posed this question for years—starting with CAPS 1, a pilot study, and then progressing from a single-center to multi-institutional studies with CAPS 2–4. According to Goggins, the CAPS program seeks ways to identify and treat precancerous lesions before they become lethal. Inclusion criteria have changed. At first, participants had to be aged 50 years or older, and they had to have three blood relatives (with at least one first-degree relative) with pancreatic cancer. For CAPS 4, which launched in 2008 with a completion date of 2016, participants needed only two blood relatives with the disease, at least one of whom must be a first-degree relative. The CAPS 4 inclusion criteria also cover a variety of inherited factors, including familial Peutz–Jeghers syndrome and germline mutations in BRCA1, BRCA2, and p16/CDKN2A (a gene predisposing to familial atypical multiple-mole melanoma), specifically among individuals with at least one relative with pancreatic cancer. Among all the factors, family history and Peutz–Jeghers syndrome contribute the most risk by far. Contributions from germline mutations, however, aren’t well understood, and the role of age is likewise uncertain. “Below 50 might be too young for screening,” Goggins said. From current experience, “we think 55 might be the better cutoff, but we’re not sure yet.”

Whether high-risk screening through CAPS and other academic programs reduces pancreatic cancer mortality or even incidence remains unknown. The experience with colorectal and other cancers shows that the mortality benefits from screening can take decades to appear, and meanwhile scientists can only assume that preventing carcinoma in situ in the pancreas by finding and removing precancerous lesions is worthwhile, Goggins said.

Screening for Sporadic Tumors
Moreover, by focusing only on high-risk individuals, current screening programs miss almost all potential cases. Roughly 90% of all pancreatic cancers are sporadic—occurring in patients with no known genetic risk factors. But how to screen for potentially lethal sporadic tumors is not clear. “And this is something you don’t want to get wrong,” Brentnall said. “We need tests with very high specificity so that we don’t wind up with false-positive diagnoses. False positives are very expensive to work up, and they terrify patients.” According to Brentnall, sporadic tumor screening should be limited to individuals with nonheritable risk factors, such as smoking, adult-onset diabetes, and chronic pancreatitis. These factors can produce two- to fourfold elevations in the likelihood of developing the illness, she said. John Neoptolemos, M.D., a surgeon and professor at the University of Liverpool in the UK, added that clinicians might also look beyond traditional symptoms, such as abdominal pain and jaundice, to consider chronic indigestion, back pain, and other potentially important complaints. “That’s a group that could benefit from more CT scanning,” he said.

Sporadic pancreatic tumors also show up during imaging for other problems. But more often, imaging reveals tiny cysts on the pancreas without obvious clinical significance, and what to do about these “incidentalomas,” as Goggins calls them, has become a big issue. Some cysts might remain stable, whereas others progress to cancer, and meanwhile overtreatment should be avoided if possible, Goggins said. Neoptolemos said that researchers at his facility are developing algorithms to help determine which incidentally discovered cysts should be removed. Biomarkers such as CA19-9 and CEA (carcinoembryonic antigen) can offer some insight in that regard, he said, but they don’t reliably distinguish among malignant, premalignant, and benign cysts. Neoptolemos relies on ultrasound to examine the cyst lining for nodules, which suggest the growths could be turning malignant. “All of this is time consuming, and that’s why we’re trying to develop protocols,” Neoptolemos said. “For instance, if the cyst is less than 1 cm, and it has a smooth lining, we might rescann in 2 years if the patient is less than 60 years old. If the patient is older than that, we might scan in 6 months. This is all guesswork right now. We need better biomarkers to help us understand that’s happening in the cyst.”

According to Goggins, evidence suggests that benign cysts don’t express KRAS or P53 mutations, whereas the more dangerous cysts do. Moreover, KRAS mutations appear to dominate in early-stage neoplasia, whereas P53 mutations dominate as growths become more aggressive. Johns Hopkins researchers are now experimenting with how these biomarkers—obtained from pancreas fluid in the duodenum—to avoid injuring the pancreas itself—can help in deciding how often patients should be screened. “We think that by combining these mutational data with imaging, we’ll be able to make this determination,” he said. “This is the primary way that the CAPS-based studies are going to advance screening—not by using blood biomarkers that aren’t specific enough to be useful.”

But Neoptolemos countered that researchers shouldn’t dismiss blood biomarkers for screening yet. For instance, high-grade PanINs appear to go into circulation, he said, so a serum test could detect them. Furthermore, groups of weak blood biomarkers could be lumped together into panels with a combined accuracy of more than 99%, according to Matthew Firpo, M.D., a research assistant professor in surgery at the University of Utah. “Blood biomarkers may be premature, but overall we’re seeing some exciting breakthroughs in early detection,” Brentnall said. “Pancreatic cancer is a terrible disease, and the emotional trauma it inflicts on family member is similar to the trauma of murder. And that illustrates why people working in this area are so dedicated.”