Blinded by the Light: Molecular Imaging in Pancreatic Adenocarcinoma

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The early detection and optimal perisurgical management of pancreatic adenocarcinoma are paramount goals in our quest to increase cure rates in this lethal malignancy. Molecular imaging techniques may be the conduit through which new genomic and proteomic discoveries about this disease are brought to the clinic.

In this issue of Clinical Cancer Research, Bausch and colleagues (1) bring a novel molecular imaging probe based on Plectin-1 (Plec1) expression to bear on pancreatic ductal adenocarcinoma (PDA), with ramifications for both finding malignant lesions earlier and increasing the sensitivity of staging of the disease peripherally.

In 2010, more than 43,000 patients will be diagnosed with PDA and nearly 37,000 will die of the disease in the United States alone (2). Many attribute this high mortality to the fact that most cases of pancreatic adenocarcinoma are diagnosed after the disease has spread beyond the limits of surgical resection.

Imaging plays an important role in cancer management and has been successfully deployed for screening in the asymptomatic patient, making a diagnosis after prompts from signs or symptoms, and assessing the extent of disease (staging) to direct therapy. To date, the use of imaging in pancreatic cancer has been limited to diagnosis and staging, predominantly with multidetector dynamic-phase computed tomography (CT), endoscopic ultrasound (EUS), endoscopic retrograde cholangiopancreatography, and, more recently, magnetic resonance cholangiopancreatography.

Preoperative staging of pancreatic cancer is done to determine resectability. Resectability is governed by two cardinal precepts: the lack of extrapancreatic disease, and the absence of local vascular invasion (3). Dynamic-phase CT scanning of the abdomen, frequently with adjunctive EUS, is used for staging. Together, these modalities are reported to accurately predict resectability in 85–90% of patients. According to published reports, the usual reason for aborting resections is a finding of occult liver or peritoneal metastases and, less commonly, unanticipated vessel involvement. Theoretically, radionuclide imaging [positron emission tomography or ligand-based gamma emission scans such as singlephoton emission CT (SPECT)] could detect extrapancreatic disease; however, to date, technical issues limit the detection of subcentimeter lesions, where this could be most helpful. A prime example is the reported failure of 111In-labeled B72.3 monoclonal antibody to improve staging of patients with colorectal cancer (4).

Screening for pancreatic adenocarcinoma is challenging. A test would have to be nearly 100% sensitive and specific in order to be cost-effective, and thus current efforts are focused on developing biomarkers to enrich for high-risk subgroups in which screening can be justified. One existing high-risk subgroup consists of families with inherited forms of pancreatic cancer.

Imaging with EUS-based screening of high-risk family cohorts is pursued at some centers, but it remains investigational and has not yet shown a survival benefit for screened patients (5). Reports from EUS-based programs do drive home three important lessons: 1) EUS is an operator-dependent procedure with largely unstudied interrater reliability, 2) the decision of when and how to intervene based on suspicious EUS findings often presents a clinical conundrum, and 3) many individuals in these high-risk families develop premalignant lesions in the pancreas, such as high-grade pancreatic intraepithelial lesions (PanINs), intraductal papillary mucinous neoplasms (IPMNs), or mucinous cystic neoplasms (MCNs) (6, 7). Cyst aspiration for carcinoembryonic antigen can discriminate between benign and malignant cysts (8), but to date there is no test available to determine the malignant potential of benign lesions.

The work of Bausch et al. in this issue of Clinical Cancer Research picks up where that of Kelly and colleagues left off in 2008 (9). In this earlier work the authors had screened a phage display library against a mouse model of pancreatic cancer (10), and identified peptides that bound to Plec1. Bausch and colleagues first further define the distribution of Plec1 expression in normal pancreas, pancreatitis, PanIN (precursor lesions to PDA; ref. 11) of various grades, and PDA. They show that Plec1 is expressed in PanIN III (high-grade, incipient neoplasia) and PDA, but not in the more benign conditions, notably including earlier PanIN lesions. They employ a tissue microarray to further delineate the distribution of Plec1 expression in human tissue, and find...
strong Plec1 expression in benign tissues of the genitourinary system as well as in carcinomas of the aerodigestive tract. They then conjugate Plec1-binding peptides to $^{111}$In-labeled nanoparticles (yielding $^{111}$In-tPTP) to render them detectable by single-photon SPECT/CT imaging, and persuasively demonstrate the ability to visualize orthotopically implanted primary pancreatic ductal adenocarcinoma (PDAC) as well as metastases in the liver of living animals.

The strengths of this work lie in the apparent specificity of the marker (Plec1) for high-grade PanIN lesions and PDAC (as well as possibly other adenocarcinomas). The most facile clinically relevant interpretation of this finding is that tissues labeled with the $^{111}$In-tPTP reagent are likely to be either frank PDAC or high-grade PanIN lesions and should be surgically removed, given that the data presented herein suggest that false positives should be low, in turn resulting in a high positive predictive value for a positive finding. Less well described are factors addressing the negative predictive value of the approach.

The authors allude to both screening and staging implications for the $^{111}$In-tPTP approach. As noted above, staging of PDAC (especially detection of early liver metastases) has improved greatly with the development of dynamic-phase, multidetector CT scanning and EUS. Until SPECT imaging can identify subcentimeter lesions, however, it is unlikely that this imaging strategy will be able to influence management. Another possible tactic might be to deploy hand-held scintillation devices to improve intraoperative identification of occult metastases (12).

That being said, the work described by Bausch and colleagues does open interesting and potentially important avenues into more functional screening approaches, as currently employed in high-risk individuals and families. Most high-risk screening clinics use an eight- to 10-fold above-average increased risk for PDA as a reasonable cutoff to justify their intensive EUS-based programs. After completing genetic counseling and (occasionally) testing, clinicians will typically employ serial EUS or MRI studies. As noted above, high-risk individuals can present with PanINs, IPMNs, and MCNs. Because Plec1 can distinguish between low- and high-grade PanINs, it is possible that the marker could also discriminate between less- and more-aggressive IPMNs and MCNs. This could easily be studied on archival tissue, and we hope that investigators will explore this in the future. $^{111}$In-tPTP could be compared in parallel with the EUS-biopsy-resection program algorithm to evaluate the sensitivity and specificity of the technique in the real world. In this scenario, imaging for Plec1 could define the optimal time to surgically intervene for lesions of uncertain malignant potential (see Fig. 1).

Although there are many limits to the immediate applicability of the $^{111}$In-tPTP approach, the central strengths of the work of Busch and colleagues remain encouraging. Recent findings suggest that the central genomic events in PDA arise more than a decade before the disease clinically declares itself (13). It is hoped that as we learn more about the molecular pathologies of the PDA genome, transcriptome, and proteome, both our understanding of their role in PDA and our ability to deploy new ideas in the treatment of this disease will grow exponentially. In this elegant body of work, which moves from animal model to proteomics, and from cutting-edge imaging to clinically deployable assay, Bausch and colleagues provide a template for further molecular-based imaging in this disease.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

Received November 9, 2010; accepted November 12, 2010; published OnlineFirst November 24, 2010.
References

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Access the most recent version of this article at:
doi:10.1158/1078-0432.CCR-10-2825

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