Blinded by the Light: Molecular Imaging in Pancreatic Adenocarcinoma
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Summary: 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 in the disease are brought to the clinic.
In this issue of *Clinical Cancer Research*, Bausch *et al.* 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 perisurgically (1).

Over 43 thousand patients will be diagnosed with PDA and nearly 37 thousand will die of the disease in the US alone in 2010 (2). Many attribute this high mortality to the fundamental observation 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, for diagnosis following prompts from signs or symptoms, and to assess 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) and endoscopic retrograde cholangiopancreatography (ERCP). More recently magnetic resonance cholangiopancreatography (MRCP) is being used.

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

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

Imaging using EUS based screening of high risk family cohorts is pursued at some centers but remains investigational, and has not yet demonstrated a survival benefit to screened patients (5). These EUS based programs do drive home three important lessons; 1) that EUS is an operator-dependent procedure with largely unstudied inter-rater reliability, 2) that the decision of when and how to intervene on suspicious EUS findings often presents a clinical conundrum and 3) many individuals in these families develop premalignant lesions in the pancreas, such as high grade pancreatic intraepithelial lesions (PanINs), intraductal papillary mucinous neoplasm (IPMN) or mucinous cystic neoplasms (MCN) (6),(7). Cyst aspiration for CEA can discriminate between benign and malignant cysts (8), but there is no test yet 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 et al. left off in 2008 (9). The authors’ previous work had screened a phage display library against a mouse model of pancreatic cancer (10), and identified peptides that bound to Plec1. Bausch et al. first further define the distribution of Plec1 expression in normal pancreas, pancreatitis, PanIN (precursor lesions to PDA (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, importantly 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 Indium 111-labeled nanoparticles (yielding 111In-tPTP) to render them detectable by single photon SPECT/CT imaging and persuasively demonstrate the ability to visualize orthotopically implanted primary PDAC (in the pancreas) as well as metastases in the liver, in 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 111In-tPTP reagent are likely to be either frank PDAC or high grade PanIN lesions and should be surgically removed, since the data presented herein suggest 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 111In-tPTP approach. As noted above, staging of PDAC, (especially detection of early liver metastases) has improved greatly with dynamic phase, multidetector CT scanning and EUS. Until SPECT imaging can identify subcentimeter lesions, it’s unlikely that this imaging strategy could impact management. Another tactic however might deploy hand held scintillation devices to improve intraoperative identification of occult metastases (12).

That being said, the work described by Bausch et al. does open interesting and potentially important avenues into more functional screening approaches, currently employed in high risk individuals and families. Most high risk screening clinics use an eight to ten fold above average increased risk for PDA as reasonable cut off to justify their intensive EUS-based programs. After genetic counseling and occasionally testing, clinicians will typically employ serial EUS or MRI studies. As noted above, these individuals can present with PanINs, IPMNs, and MCNs. Since 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 the investigators will explore this in the future. 111In-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 on lesions of uncertain malignant potential (See Figure 1).

While there are many limits to the immediate applicability of the 111In-tPTP work, the central strengths of Busch et al. remain encouraging. Recent work suggests that the central genomic events in PDA arise more than a decade before the disease clinically declares itself (13). As we learn more about the molecular pathologies of the PDA genome, transcriptome and proteome, the need to first understand their role in PDA, and then deploy new ideas in the treatment of the disease will hopefully grow exponentially. In this elegant body of work moving from animal model to proteomics to cutting edge imaging to clinically deployable assay, Bausch et al. provide a template for further molecular based imaging in this disease.
References

Figure Legend

Figure 1: Potential Application of Molecular Imaging in a high risk cohort undergoing screening.
High risk family in screening program

EUS/MRCP screening

Normal

Continued surveillance

Suspicious for premalignant lesion

Molecular imaging

High risk

Consider early resection

Low risk

Continued surveillance

Low risk

Continued surveillance

High risk family in screening program

Normal

Continued surveillance

Suspicious for premalignant lesion

Molecular imaging

High risk

Consider early resection

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