Combining in Vitro Diagnostics with in Vivo Imaging for Earlier Detection of Pancreatic Ductal Adenocarcinoma: Challenges and Solutions¹

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Pancreatic ductal adenocarcinoma (PDAC) is the fourth-leading cause of cancer-related death in the United States and is associated with a dismal prognosis, particularly when diagnosed at an advanced stage. Overall survival is significantly improved if PDAC is detected at an early stage prior to the onset of symptoms. At present, there is no suitable screening strategy for the general population. Available diagnostic serum markers are not sensitive or specific enough, and clinically available imaging modalities are inadequate for visualizing early-stage lesions. In this article, the role of currently available blood biomarkers and imaging tests for the early detection of PDAC will be reviewed. Also, the emerging biomarkers and molecularly targeted imaging agents being developed to improve the specificity of current imaging modalities for PDAC will be discussed. A strategy incorporating blood biomarkers and molecularly targeted imaging agents could lead to improved screening and earlier detection of PDAC in the future.

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Pancreatic ductal adenocarcinoma (PDAC), which accounts for approximately 90% of all pancreatic neoplasms (1), is the fourth-leading cause of cancer-related deaths in the United States, with more than 37 000 patients dying of pancreatic cancer every year. Unfortunately, the prognosis is almost universally poor, with an overall 5-year survival rate of approximately

5% and a median survival of less than 6 months (2–4). Incidence increases with age, and most patients are diagnosed with PDAC after age 50 (median age at diagnosis is 71 years) (5).

In the majority of patients, the development of pancreatic cancer involves the progression through precursor lesions termed pancreatic intraepithelial neoplasia (PIN) and the accumulation of an increasing number of genetic aberrations (6). PIN is graded I–III, with the highest grade (carcinoma in situ) being grade III. PIN grades I and II lesions are frequently observed in normal pancreata and pancreatitis and are often associated with point mutations in the *K-ras* oncogene, overexpression of the human epidermal growth factor receptor type 2/*neu* gene product, and inactivation of the *p16* tumor suppressor gene. Mutations in the *p53*, *DPC4*, and *BRCA2* tumor suppressor genes are seen in later stage PINs and pancreatic adenocarcinoma. These genetic alterations are just a small subset of a much larger group of genetic changes affecting a core group of signaling pathways and processes that are altered in pancreatic cancer (7). These changes may serve as targets for screening and earlier detection of pancreatic carcinoma. For example, overexpression of plectin-1, a cytolinker in the plakin family that is currently being investigated in human clinical trials, is seen not only with invasive pancreatic carcinoma, but also with PIN grade III (8). Another example is vascular endothelial growth factor, the principal mediator of angiogenesis, which is upregulated in response to hypoxia, growth factors, and oncogenic proteins (eg, transforming growth factor β , epidermal growth factor, and rat sarcoma). Vascular endothelial growth factor is overexpressed in more than 90% of pancreatic cancers (9).

It is estimated that at least 10% of pancreatic cancers are inherited (10). This includes patients with one of several known familial cancer syndromes, such as Peutz-Jeghers syndrome, familial atypical multiple mole melanoma, hereditary breast-ovarian cancer, hereditary nonpolyposis colorectal carcinoma, and familial adenomatous

polyposis, all of which are associated with an increased risk of pancreatic cancer (11). These syndromes account for 15%–20% of patients with inherited pancreatic cancer (12). The majority of familial pancreatic cancer, diagnosed as having two or more affected first-degree family members with PDAC, is caused by unknown genetic mutations. The risk of PDAC in first-degree relatives is higher with a greater number of affected family members. The National Familial Pancreas Tumor Registry reported cumulative lifetime risks of developing pancreatic cancer of 8%–12% and 16%–30% for patients with two and three affected first-degree relatives, respectively (13). In addition to people with familial cancer syndromes, individuals with hereditary pancreatitis and cystic fibrosis also have an inherited predisposition to pancreatic cancer. Finally, even without one of the aforementioned syndromes, the risk of developing pancreatic cancer is greater for individuals with a single affected first-degree relative and in individuals with adult-onset diabetes, where the incidence is approximately one in 300 (14,15).

Treatment and Diagnostic Challenges of PDAC

Advances in chemotherapy and radiation therapy, including in the adjuvant setting, have led to modest improvements in the 5-year survival rate of pancreatic cancer (16). Surgery remains

Essentials

- Pancreatic ductal adenocarcinoma (PDAC) is most commonly diagnosed at an advanced stage, at which point it is associated with a dismal prognosis with few effective treatment options and an overall 5-year survival rate of approximately 5%.
- Currently, there are no screening approaches suitable for the general population; patients deemed to be at high risk for developing PDAC are screened with a multimodality approach of endoscopic US, magnetic resonance cholangiopancreatography, and/or endoscopic retrograde cholangiopancreatography.
- A strategy incorporating blood biomarkers and molecularly targeted imaging agents could lead to improved screening and earlier detection of PDAC in the future.
- Numerous blood biomarkers are being investigated for the earlier detection of PDAC, many of which are associated with improved sensitivity and/or specificity for PDAC when compared with the only clinically available, Food and Drug Administration–approved blood biomarker for PDAC, CA19-9.
- Novel molecularly targeted imaging agents are being developed in an effort to improve the specificity of imaging modalities currently used to detect pancreatic cancer, which include US (transabdominal and endoscopic), CT, MR imaging, and PET.

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Abbreviations:

ERCP = endoscopic retrograde cholangiopancreatography
 FDA = Food and Drug Administration
 FDG = 18 fluorine fluorodeoxyglucose
 MRCP = MR cholangiopancreatography
 PIN = pancreatic intraepithelial neoplasia
 PDAC = pancreatic ductal adenocarcinoma

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the only current treatment affording potential long-term survival for PDAC. The 5-year survival rate has been reported to be as high as 18% in a large single institution experience of patients undergoing pancreaticoduodenectomy for PDAC (17). Nevertheless, very few patients are cured with surgery even when the surgical margins are free of tumor. This is due in part to a unique characteristic of the tumor biology of PDAC, namely its propensity to spread at a very early stage beyond the pancreas via perineural pathways (18,19). The autonomic nerve fibers of the celiac and mesenteric plexus form conduits for retrograde extension of tumor, and a variety of neurotrophic factors have been implicated in facilitating this mode of extrapancreatic invasion (20,21).

Unfortunately, the diagnosis of PDAC is often made at an advanced stage and fewer than 20% of patients are suitable candidates for surgical resection. Factors contributing to a delay in diagnosis include the inconsistent and vague symptoms related to the disease, difficulties in visualizing lesions at an early stage, and the lack of specific and sensitive diagnostic serum markers.

Screening for PDAC

The overall 4-year postoperative survival rate for patients undergoing resection of small (< 2 cm) stage I ductal adenocarcinomas of the pancreas has been reported at 78% (22). Forty-two percent of those patients were asymptomatic (22). These data suggest that detecting pancreatic cancer prior to the onset of symptoms might improve the dismal prognosis associated with the disease. Ideally, for early detection of pancreatic cancer in the general population, the test would need to be low cost, non- or minimally invasive, and necessarily have very high specificity. However, it is currently neither advisable nor cost-effective to screen the general population given the low prevalence of the disease, the relatively low diagnostic accuracy of present detection methods, the absence of promising treatment modalities other than

surgery, and the increased morbidity associated with false-positive results (23–25). A Markov model of PDAC demonstrated a net decrease in life expectancy of 3 days for men and 4 days for women when a magnetic resonance (MR) imaging-based screening strategy was used for average-risk patients, primarily driven by morbidity associated with unnecessary pancreatic surgeries (25). Given the aforementioned reasons, efforts are currently focused on surveillance for individuals at high risk for developing pancreatic cancer (26). It has been recommended that people with a greater than 10-fold increased risk of developing pancreatic cancer be screened. This includes individuals with familial pancreatic cancer. The guidelines for these genetically susceptible individuals are in a state of flux. However, most programs would recommend screening for individuals who have two or more family members with pancreatic cancer (with at least one of these being a first-degree relative). Surveillance is cost-effective in individuals with a lifetime risk of pancreatic cancer exceeding or equal to 15% (including individuals with *p16* mutations or Peutz-Jeghers syndrome) (27). Individuals who have a life-time risk of less than 15% (eg, individuals with *BRCA1/2* mutations, Li-Fraumeni syndrome, Lynch syndrome, or familial adenomatous polyposis) but who have at least one relative with pancreatic cancer could also be considered for screening (28,29). In such a setting, risks are cumulative, with the personal risk of the mutation carrier compounded by the risk conferred by an affected first degree relative. Other risk factors, such as smoking or adult-onset diabetes, can also play into the risk assessment of an individual.

At present, a multimodality screening approach of endoscopic ultrasonography (US), MR cholangiopancreatography (MRCP), and/or endoscopic retrograde cholangiopancreatography (ERCP) appears to be the most effective method to screen for pancreatic cancer in high-risk patients (28,30). However, such an approach is usually relegated to surveillance centers of

expertise. Endoscopic US, the baseline test performed in most pancreatic cancer surveillance programs, is subjective in nature and needs to be performed by gastroenterologists with specialized training. Computed tomography (CT) is not currently used in surveillance of the pancreas because it cannot depict the precancerous changes or very early cancers that initially occur in the small- and medium-size ducts; moreover, it exposes individuals to radiation. Because surveillance of high-risk individuals is relegated to specialized centers of expertise, continued efforts are needed to find a more practical screening approach for detecting pancreatic cancer at earlier stages for the community at large. If an imaging test was sufficiently accurate and inexpensive, then high-risk patients would not need to seek specialized centers and moderate-risk patients with nonhereditary risk factors, such as new adult-onset diabetes, might benefit from screening protocols. Average-risk populations might benefit from an approach that utilizes serum tumor markers, given their low cost and wider availability.

Blood Biomarkers for Early PDAC Detection

Many blood tests have been evaluated for detection of pancreatic cancer but none have been sufficiently accurate for screening in average- or even moderate-risk individuals (31). Currently, CA 19-9 is the only Food and Drug Administration (FDA)-approved clinical biomarker for pancreatic cancer. However, it is mostly used as a prognostic marker for disease monitoring. CA 19-9 is a carbohydrate antigen that is present on various mucins secreted by pancreatic cancer cells (31). The clinical utility of CA 19-9 as a diagnostic marker has proven to be ineffective due to its low sensitivity (60%–70%) and poor specificity (70%–85%) (31). Because of the low prevalence of pancreatic cancer in the general population, a clinically acceptable biomarker would need to have near-perfect specificity ($\geq 99\%$). For high-risk patients, a sensitivity of more than 90% and a specificity of more than

90% have been suggested (32). Kim et al evaluated CA 19-9 for screening asymptomatic people for pancreatic cancer and found an unacceptably low positive predictive value of 0.9% when a level of greater than 37 U/mL was used (33). Carcinoembryonic antigen and CA-125 are serum antigens that are occasionally elevated in pancreatic cancer; however, their utility as diagnostic biomarkers is even less informative than that of CA 19-9 for pancreatic cancer (34).

Many candidate biomarkers for pancreatic cancer have been described in the literature, but none have reached the clinic largely due to the overlap of molecular signatures between pancreatic cancer and chronic pancreatitis. Ten percent of the US population has occult chronic pancreatitis at autopsy, so this overlap between cancer and benign diseases of the pancreas is important (35–37). Extensive research is ongoing to address this challenge, especially through the use of newer technologies, including quantitative proteomics, the measurement of analytes such as microRNA, metabolites, autoantibodies, DNA methylation, *K-ras* mutation, circulating tumor cells, and assessment of the microbiome.

Protein

Protein is the most common analyte for blood testing. Recent investigations using mass spectrometry-based quantitative proteomics for large-scale protein profiling of tumors, tumor cells, or bodily fluids in both pancreatic cancer patients and control subjects have identified many biomarker candidates. However, further characterization of these putative biomarkers in blood is challenging. Antibody-based techniques, such as enzyme-linked immunosorbent assay, represent the current reference standard for protein biomarker measurement in the blood. However, the creation of high-quality antibody assays requires extensive time, resources, and effort, leading to a bottleneck in biomarker development. Targeted proteomics is an emerging technology that is playing an increasingly important role to facilitate disease biomarker

development. A selected reaction monitoring-based targeted proteomics platform was recently developed to directly detect candidate biomarker proteins in plasma and evaluate their clinical utility for pancreatic cancer detection (38). By using this simple and robust selected reaction monitoring-based multiplexed assay, five pancreatic cancer biomarker candidates (14–3-3 protein sigma, gelsolin, lumican, transglutaminase 2, and tissue inhibitor of metalloproteinase 1) were tested in plasma from a clinically well-characterized pancreatic cancer cohort. The study developed a biomarker panel of gelsolin and lumican with 80% sensitivity and 95% specificity in separating early-stage pancreatic cancer from healthy control subjects and patients with chronic pancreatitis (38).

Plasma or serum represents an ideal diagnostic specimen for clinical tests due to its low cost and easy accessibility. Unfortunately, it is technically difficult to study low abundance proteins in blood because of its enormous protein complexity. Extensive separation at both protein and peptide level by using electrophoresis and multidimensional liquid chromatography is one way to enhance the identification of low abundant proteins in serum and/or plasma. By using this approach, a large-scale quantitative proteomics study was performed to search for the plasma protein alterations associated with PDAC, and a biomarker panel of “tissue inhibitor of matrix metalloproteinase-1 (TIMP-1) or intercellular adhesion molecule 1 (ICAM-1)” was identified with 75% sensitivity and 95% specificity in distinguishing pancreatic cancer from the nonpancreatic disease control subjects and chronic pancreatitis control subjects (39). In another study in which a bead-based multiplex immunoassay was used, a biomarker panel of CA 19-9, ICAM-1, and osteoprotegerin could detect pancreatic cancer with 78% sensitivity and 94% specificity, and a biomarker panel of CA 19-9, carcinoembryonic antigen, and TIMP-1 demonstrated 71% sensitivity and 89% specificity in detecting PDAC (32). While these biomarker panels

perform better than CA 19-9, the specificity remains too low for use in the screening setting.

MicroRNA

MicroRNAs are small noncoding RNAs (approximately 22 nucleotides) involved in posttranscriptional gene regulation. The potential roles of microRNAs as oncogenes and tumor suppressor genes have provided a new perspective to biomarker research. Recent microRNA studies suggest the potential of using microRNAs as diagnostic biomarkers. Plasma miR-221 was shown to be significantly higher in PDAC and could separate PDAC from healthy control subjects with sensitivity of 25%, specificity of 95%, and area under the receiver operating characteristic curve (AUC) of 0.74 (40). A panel of four plasma microRNAs, including miR-21, miR-210, miR-155, and miR-196a, could separate pancreatic cancer from control subjects with sensitivity of 64%, specificity of 89%, and AUC of 0.78 (41). However, it should be noted that benign pancreatic diseases were not included in the control groups from the above two studies. Inclusion of benign pancreatic processes in these studies would likely decrease the AUC. Recent studies using salivary RNA measurements have been intriguing. Four messenger RNA biomarkers could differentiate patients with PDAC from subjects without cancer, including those with pancreatitis and normal control subjects, with 90% sensitivity and 95% sensitivity. These data are now being expanded (42).

DNA Methylation

Cancer-specific DNA methylations can be detected in tumor tissue, blood, and other bodily fluid, providing the feasibility of its utility in diagnosis. DNA methylation has been a longstanding subject of interest in malignancies. Studies have been performed to investigate pancreatic cancer-specific promoter hypermethylation in plasma and to explore it as a diagnostic biomarker. Plasma NPTX2 methylation distinguished pancreatic cancer from pancreatitis with sensitivity of 80% and specificity of 76% (43). In another study,

methylation of 14 gene promoters differentiated PDAC from chronic pancreatitis with 91.2% sensitivity and 90.8% specificity (44). With the emergence of current epigenetic profiling technologies, recent studies have focused on investigation of empirically driven DNA methylations associated with cancer. It is expected that new hyper- or hypomethylated targets associated with cancer will be discovered and investigated for their utility in diagnosing PDAC.

Other Biomarkers

Other analytes that have been explored as diagnostic biomarkers for PDAC include autoantibodies, metabolites, gene mutations, circulating tumor cells, and oral microbiome (45). In addition to blood, plasma, and serum, other specimen types, such as pancreatic juice, cystic fluid, urine, and tissue from needle biopsies, have also been explored for diagnostic biomarkers. The studies related to these other analytes and specimen types are beyond the scope of this review article.

Considerations on Cost-Effectiveness of a Blood Biomarker Test

In the development of a blood test for earlier detection of PDAC, a key factor to be considered is whether the blood test is cost-effective. In fact, cost-effectiveness studies performed by assessing the third-party payer costs of the blood test, imaging tests, subsequent medical and surgical management that includes morbidity and mortality versus life-years saved suggest that the specificity of a test for earlier detection of PDAC would need to be very high (25). This is because PDAC is a relatively rare disease. For example, a blood test with 98% specificity and 100% sensitivity performed in an average-risk population would identify one individual with PDAC out of 10000 screened people, but 200 individuals would have a false-positive test. The cost of working up the false-positive tests, not to mention the psychological stress to the cancer-free individual, would be prohibitive. If the incidence of pancreatic cancer is higher, such as in patients with adult-onset

diabetes (one in 300 incidence) and in familial pancreatic cancer individuals, then the test becomes more cost-effective (14,15). As such, the creation of a screening test for diagnosing pancreatic cancer would need to be tailored to the population that is being tested: (a) general population with average (eg, low) risk would need to have a screening test with almost 100% specificity; (b) moderate-risk population, such as asymptomatic patients with adult-onset diabetes, would need to have a screening test with high specificity that approaches 98%–99%; (c) a diagnostic test for symptomatic patients could have somewhat reduced specificity to provide high sensitivity; and (d) high-risk patients, who have a genetic susceptibility to the disease, need to have a high sensitivity screening test (greater than 90%–95%) while the specificity could be somewhat relaxed. In the latter setting, individuals with a genetic susceptibility of 15% or higher are frequently in endoscopic surveillance due to their high risk and as such, a screening test in this cohort would need to distinguish those patients who could forego endoscopic US (the mainstay of most PDAC surveillance programs) versus those who would need to undergo imaging. In this setting, it would be imperative not to miss a pancreatic cancer; however, a false-positive test would only lead to the endoscopic US that would have been performed anyway.

For researchers who are developing PDAC blood tests, not only is it important to tailor the performance characteristics to match the pretest probability of having pancreatic cancer, but also to test the candidate biomarker in the setting in which it would be used. Control subjects should include symptomatic patients if the test is designed as a diagnostic. Diabetic patients without pancreatic cancer would be included as control subjects if the screening test is designed for screening adult-onset diabetes, and a large number of benign pancreatic diseases would need to be included for a screening the general population. In addition, control subjects should be derived from a variety of geographic locations, as

there is heterogeneity in the diseased control subjects that can affect the overall specificity. Inherent in the cost-analysis of any blood test would be the requirement for a confirmatory imaging test. Importantly, if a confirmatory imaging test were inexpensive, easily performed, and noninvasive, then the performance requirements of a pancreatic cancer-screening test could be reduced.

Clinically Available Imaging Modalities for Diagnosing PDA

Transabdominal and Endoscopic US

According to the American College of Radiology appropriateness criteria, a multiphasic CT is the best first test for patients with painless jaundice, the presenting feature in the majority of patients with PDAC located in the head of the pancreas. Despite this, transabdominal US is often the initial investigation performed in patients presenting with upper abdominal pain or jaundice. The technique is inexpensive, widely available, and extremely sensitive for detecting biliary obstruction (46). However, the sensitivity of transabdominal US for detecting PDAC varies widely depending on the size of the tumor, ranging from 95% in tumors larger than 3 cm to 50% in tumors smaller than 1 cm (47). In a recent retrospective review of 189 patients with pancreatic head cancer, the detection rate of pancreatic cancer with transabdominal US was 82.0%, which was lower than that with CT (93.1%) and endoscopic US (94.7%) (48).

Focal lesions of the pancreas are usually hypoechoic or cystic on transabdominal US images. It is difficult to differentiate adenocarcinoma from focal inflammatory masses secondary to chronic pancreatitis, endocrine tumors, or other more rare diseases based on anatomic B (bright)-mode imaging. Figure 1 illustrates several mimics of PDAC on US images. The introduction of contrast medium increases the diagnostic accuracy of transabdominal US. By using an intravenous contrast agent, contrast material-enhanced US can

Figure 1: Mimics of PDAC on transabdominal US images. **(a)** Image in 60-year-old woman with history of breast cancer and new abdominal pain shows 1.2-cm hypoechoic metastasis (arrow) in the head of the pancreas. **(b)** Image in 69-year-old man with history of hepatitis B undergoing screening US for hepatoma. An approximately 1.3 × 2.4-cm ill-defined hypoechoic region (arrow) is visualized in the uncinate process, which represents a normal variant secondary to a relative paucity of fat. **(c)** Power Doppler US image in 23-year-old woman with abdominal pain shows heterogeneously hypoechoic mass (arrow) with cystic components and no significant internal vascularity in the body of the pancreas, representing a solid and pseudopapillary neoplasm of the pancreas.

provide dynamic information regarding the macro- and microcirculation of focal lesions and of normal parenchyma (49). In the vascular phase, tumor vessels can be seen in or around the lesion in approximately 80% of patients with pancreatic cancer (50). During the perfusion phase of contrast-enhanced US, most PDACs are hypoenhancing or demonstrate irregular heterogeneous enhancement (50,51). Poorly differentiated adenocarcinoma may show a slight homogeneous enhancement pattern or heterogeneous enhancement (51,52). For the diagnosis and differentiation of pancreatic malignancies, transabdominal contrast-enhanced US has yielded results comparable to, or better than, those of many other diagnostic modalities (46,53–55). In particular, contrast-enhanced US was able to differentiate between focal pancreatitis and

pancreatic cancer—one of the major diagnostic challenges when evaluating pancreatic lesions (56). On contrast-enhanced US images, inflammatory lesions were characterized by slight continuous enhancement inside the pancreatic mass, with isovascularity to the adjacent pancreatic parenchyma. In contrast, the majority (> 90%) of PDAC was hypoechoic to the adjacent parenchyma during all phases. In that particular population, specificity and overall diagnostic accuracy for differentiating mass forming pancreatitis from malignancy were 97.8% and 96%, respectively.

The US evaluation of the pancreas can be limited by its deep location within the upper abdomen, as well as intervening bowel gas and subcutaneous fat. Endoscopic US overcomes these limitations by utilizing a transducer

placed within the stomach and duodenum in close proximity to the pancreas. With its high spatial resolution, endoscopic US is able to depict focal lesions as small as 2–3 mm, potentially enabling detection of pancreatic cancer at an early stage. Moreover, endoscopic US provides an excellent venue for sampling suspicious lesions by means of fine needle aspiration or with a biopsy needle. Studies over the last 10 years indicate that endovascular US has an accuracy of approximately 72%–94%, with the accuracy increasing in centers where gastroenterologists have specialized training in endovascular US.

Endoscopic US has been recommended as a method for screening high-risk populations for pancreatic cancer (57,58). PIN lesions occur in the small and midsize pancreatic ducts and are too small to be detected on CT or MR images. There is no imaging test that can definitively diagnose PIN stage III; however, there are non-specific changes at endoscopic US that can suggest that PIN lesions may be present in high-risk individuals. These changes are similar to the changes that are seen in chronic pancreatitis, and thus the final diagnosis of PIN lesions is made through pathologic evaluation of tissue. High-risk patients with positive endoscopic US findings usually undergo a second imaging test for further evaluation—typically MRCP or ERCP. In a prospective study using endoscopic US to screen for pancreatic cancer in high-risk individuals (57), two of 38 patients undergoing screening endoscopic US were found to have clinically significant pancreatic neoplasms and four of 38 had benign pancreatic masses. In a more recent prospective study by the same group, a neoplastic-type lesion was seen on endoscopic US images in 17 of 78 (22%) high-risk individuals, with only eight subsequently being diagnosed with pancreatic neoplasia. In addition to the high number of false-positive findings, endoscopic US is operator dependent and is associated with poor interobserver agreement for differentiating benign from malignant pancreatic lesions even in highly specialized centers (59,60).

In summary, transabdominal US is an inexpensive, widely available, and sensitive method for detecting biliary obstruction, one of the presenting features in many patients with pancreatic malignancy. However, its reliance on a good acoustic window, low sensitivity for smaller lesions, and poor specificity limit its utility for the detection of early pancreatic cancer. Endoscopic US is not limited by the deep location of the pancreas, provides a good venue for targeted lesion sampling with fine needle aspiration, and can depict smaller pancreatic lesions better than almost any other imaging modality. Its main limitation is that it is an invasive procedure, and it is also associated with poor interobserver agreement for differentiating benign from malignant pancreatic processes. US contrast agents improve the sensitivity of both transabdominal and endoscopic US. However, the specificity of contrast-enhanced US for differentiating benign from malignant pancreatic lesions is relatively low. Improving the specificity of US techniques would greatly increase the usefulness of the imaging modality for the early detection and characterization of pancreatic lesions.

Improving the Specificity of US with Molecularly Targeted Contrast Agents

The use of molecularly targeted contrast microbubbles as molecular probes has the potential to improve the sensitivity and specificity of contrast-enhanced US. Targeted microbubbles are created by attaching disease-specific ligands such as antibodies, peptides, and other small molecules to the microbubble shell surface (61,62). These ligands promote the selective targeting and retention of the acoustically active microbubbles at sites of disease, thereby providing contrast with adjacent nondiseased tissue. The microbubbles remain within the vascular space after intravascular administration, which limits targeting to molecules that are overexpressed on the surface of endothelial cells of the tumor vasculature. Despite this apparent limitation, multiple biomarkers crucial for angiogenesis are overexpressed in the

Figure 2: Detection of an approximately 3-mm PDAC by using US molecular imaging in a PDAC mouse model. Contrast microbubbles (MB_{Thy1}) targeted at a recently identified PDAC-associated molecular marker, Thy1, specifically accumulate in a small tumor and result in substantial increase in imaging signal at the tumor focus compared with surrounding normal tissue (left). Note that there is only background signal when control microbubbles ($MB_{Control}$) were injected (right).

vasculature of many malignant tumors, including pancreatic cancer. Perhaps the best examples are the receptors of vascular endothelial growth factor. Several studies have shown successful US imaging of vascular endothelial growth factor receptor 2 (VEGFR2) in preclinical animal models of breast, colon, prostate, and pancreatic cancer (63–70). In a genetically engineered mouse model, VEGFR2-targeted US imaging allowed detection of precursor ductal carcinoma in situ and invasive breast cancer with high diagnostic accuracy, by using histologic examination as the reference standard (64). Pysz et al (63) developed a VEGFR2-targeted US imaging platform to reliably detect small foci of pancreatic cancer (< 3 mm), with a 30.8-fold increased imaging signal intensity compared with that of normal pancreatic parenchyma in a genetically engineered pancreatic cancer mouse model. Foygel et al (71) discovered and validated thymocyte antigen 1 (Thy1) as a new PDAC-associated molecular imaging target expressed on the neovasculature of pancreatic cancer (Fig 2). Expression of Thy1 was significantly increased on the neovasculature of human pancreatic adenocarcinoma compared with tissue from patients with primary chronic pancreatitis or normal pancreatic parenchyma. Subsequent in vivo imaging studies in a genetically engineered mouse model of pancreatic cancer using a novel Thy1-targeted

contrast microbubble showed 4–5.5-fold increased imaging signal intensity in foci of pancreatic cancer compared with normal parenchyma. Human toxicity and feasibility studies on VEGFR2-targeted contrast microbubbles are currently ongoing (*ClinicalTrials.gov* identification numbers NCT01253213 and NCT02142608) and will determine the sensitivity and efficacy of this novel imaging approach in a clinical setting using clinically available US imaging equipment (72). Integration of molecular imaging with endoscopic US may further show enhanced visibility of early-stage PDAC in future clinical trials and may increase interobserver agreement of endoscopic US examinations.

CT and CT Perfusion

Multiphase multi-detector row CT with intravenous contrast medium is the preferred diagnostic test for suspected pancreatic lesions. CT features of pancreatic carcinoma are variable. While the majority of pancreatic carcinomas are hypoattenuating relative to the surrounding pancreatic parenchyma, a small percentage ($\sim 5\%$) are isoattenuating (73). In addition to the variable appearance of PDAC on CT images, there are a number of lesions that have an appearance similar to PDAC (Fig 3). Several secondary signs of pancreatic carcinoma have been described to improve the diagnostic accuracy of CT for PDAC, including pancreatic ductal

Figure 3

Figure 3: Pitfalls of CT for evaluating pancreatic mass lesions. **(a)** Coronal volume-rendered CT image in 35-year-old man with midepigastric pain and jaundice thought to have PDAC given the presence of a hypoattenuating mass (arrow) in the head and uncinate process of the pancreas and associated dilation of the common bile duct (white arrowhead). The patient underwent a Whipple procedure and pathologic examination demonstrated autoimmune pancreatitis. Note the lack of dilation of the pancreatic duct (black arrowhead). **(b)** Curved planar reformatted CT image in 50-year-old man with history of alcohol abuse shows a focal hypoattenuating mass (arrow) in the tail of the pancreas secondary to focal pancreatitis. Serial CT scans over several years (not shown) showed gradual atrophy of the lesion. **(c)** Axial CT image in 49-year-old woman with gastric outlet obstruction and abdominal pain shows a focal hypoattenuating mass in the region of the head of the pancreas. The patient was initially thought to have groove pancreatitis. She subsequently underwent a Whipple procedure and pathologic examination demonstrated PDAC.

dilatation, interruption of the pancreatic duct, and distal parenchymal atrophy (Fig 4). Ahn et al (74) reported the sensitivity and specificity of focal pancreatic hypoattenuation, pancreatic duct dilation, interruption of the pancreatic duct, and distal parenchymal atrophy to be 75% and 84%, 50% and 78%, 45% and 82%, and 45% and 96%, respectively.

Intravenous contrast medium increases the difference in attenuation between a pancreatic carcinoma and the surrounding pancreatic tissue (75). The timing of image acquisition after the administration of intravenous contrast material is important. Lu et al (76) first implemented a two-phase technique and reported that the mean contrast between the tumor and pancreas during the pancreatic phase (40–70 sec after infusion of intravenous contrast material at 3 mL/sec) was significantly greater than during the hepatic phases (70–100 sec after infusion). The biphasic technique has improved the detectability of pancreatic adenocarcinoma, with sensitivity ranging from 89% to 97% (77).

CT is the reference standard for staging PDAC once the diagnosis is made. CT allows visualization of the liver

and the entire upper abdomen to evaluate for liver metastases and peritoneal seeding. CT is critical for differentiating between resectable, borderline resectable and unresectable tumors based on the extent of surrounding vascular invasion. Kaneko et al evaluated the ability to predict resectability of pancreatic carcinoma by using multidetector CT angiography. By using surgery as the reference standard, multidetector CT angiography was found to have sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 100%, 71%, 85%, 100%, and 89%, respectively (78).

In CT perfusion, functional information regarding the blood perfusion of a lesion is obtained in addition to the anatomic or morphologic information from the conventional CT (79). During CT perfusion imaging, the transit of an intravenous CT contrast medium is monitored as it passes through a region of interest. Physiologic parameters of the tissue can then be estimated, including capillary permeability, fractional intravascular blood volume, blood flow, and tissue interstitial volumes. Several studies have evaluated the use of CT perfusion imaging for assessment of PDAC (80–84). In general,

perfusion parameters of pancreatic adenocarcinoma, such as blood flow and blood volume, tend to be decreased due to the decreased vascularity relative to normal pancreatic tissue. For instance, Kandel et al showed a significant decrease in mean blood flow in 30 patients with pancreatic adenocarcinoma (32 mL/min/100 mL) compared with those with normal pancreatic tissue (75 mL/min/100 mL in the head, 94 mL/min/100 mL in the body, and 92 mL/min/100 mL in the tail) (83). Xu et al also demonstrated a significant decrease in blood flow in 40 patients with pancreatic adenocarcinoma (29.5 mL/min/100 mL) compared with normal parenchyma of 36 control patients (141.28 mL/min/100 mL for the head, 128.43 mL/min/100 mL for the body, and 135.73 mL/min/100 mL for the tail) (84).

While multidetector CT can be an excellent choice for the diagnosis and staging of pancreatic malignancies, it has several limitations that make it unsuitable as a screening modality at the level of the general population. The diagnostic accuracy is limited for small (< 1 cm) PDAC. As demonstrated through creation of campaigns such as Image Wisely and Image Gently, there

Figure 4

Figure 4: Images in 81-year-old man with ductal adenocarcinoma of the pancreatic head. **(a)** Small-field-of-view transverse CT image shows an ill-defined 2.2×2.8 -cm hypovascular lesion (white arrow) in the pancreatic head and a biliary stent in place (black arrow). **(b)** Small-field-of-view axial CT image at a slightly more superior level compared with **a** shows dilatation of the pancreatic duct (arrowheads) distal to the mass and marked atrophy of the pancreatic body and tail. **(c)** Coned-down sagittal CT image shows mass (arrow) encasing the proximal superior mesenteric artery (arrowheads), which remains patent.

are also growing concerns regarding the increased risk of developing cancer after repeated exposures to radiation from medical imaging. In addition, contrast agents currently used for CT are limited in their applicability in patients with reduced renal function. CT perfusion imaging enables detection of altered perfusion parameters and will likely translate to improved treatment monitoring. However, it is unclear whether CT perfusion imaging is sensitive enough for the early detection of pancreatic cancer. CT perfusion imaging is also associated with even higher doses of radiation than conventional CT examinations, making it unsuitable for widespread use as a screening modality. Other techniques, such as dual-energy CT, are being developed to increase the conspicuity of lesions at CT. However, additional clinical experience is needed to better characterize them (85).

Improving the Specificity of CT by Using Encapsulated Contrast Medium-targeting Biomarkers

A promising alternative to bolus injections of nonspecific contrast media is the use of intravenous contrast agents that have been encapsulated in liposomes, which are highly biocompatible and associated with less toxicity.

Studies have demonstrated the feasibility of using iodinated liposomes with micro-CT, including the ability to detect submillimeter vessels (86,87). In a similar fashion as described earlier for US, attempts have been made to improve the specificity of the technique by inserting specific ligands into the liposomal membranes (88,89). To date, there have been no reports using this technique to specifically target PDAC. In an in vitro experiment, Danila et al (90) demonstrated specific binding of anti-intercellular adhesion molecule 1 (ICAM-1)-conjugated liposomes filled with CT contrast medium to activated human coronary artery endothelial cells expressing ICAM-1. Wyss et al (91) successfully designed an E-selectin-targeted iodine-containing liposome specific for E-selectin, which is expressed on the surface of endothelial cells in response to inflammatory processes (92) or on proliferating endothelial cells (93). In vitro experiments and in vivo micro-CT imaging of human colorectal cancer (HT-29 cells)-bearing mice demonstrated accumulation of the targeted liposomes to activated vessels. Hence, the differential expression of E-selectin between proliferating and quiescent cells makes E-selectin an optimal candidate for

molecular imaging of activated vessels specifically, which may prove useful for the early detection of neoplastic processes. These studies are promising, but the use of CT as a molecular imaging modality has yet to be fully defined. The low sensitivity and need for relatively large quantities of contrast medium currently limits wider adoption of molecularly-targeted CT imaging (88,94).

ERCP Technique

ERCP is an invasive technique but remains the procedure of choice for high-resolution assessment of biliary and pancreatic ductal anatomy. Contrast material is injected directly into the pancreatic ducts under fluoroscopic guidance. Because PDAC is of ductal origin, ERCP is very sensitive (78%–95%) and specific (88%–95%) for detecting pancreatic malignancies (95,96). However, it is not as sensitive as endoscopic US. Moreover, ERCP is not suitable as a screening tool given its invasiveness and associated complications (chiefly, the risk of acute pancreatitis), which are not encountered with other noninvasive imaging modalities. Thus, ERCP is usually reserved for situations in which a therapeutic intervention could be required, such

as stent placement, when performing the diagnostic evaluation.

MR Imaging and MRCP

Relative to CT, MR imaging has the advantage of improved soft-tissue contrast resolution and no reliance on ionizing radiation. Currently, PDAC is best detected by using nonenhanced T1-weighted fat-suppressed gradient-recalled-echo imaging followed by contrast-enhanced imaging with gadolinium-based contrast agents (97–99). Normal pancreatic tissue has high signal intensity on noncontrast T1-weighted fat-suppressed images because of the presence of aqueous protein in the

acini of the pancreatic parenchyma. Normal pancreatic tissue demonstrates a uniform capillary blush immediately after contrast enhancement and fades to isointense signal relative to the liver on interstitial phase images. In contrast, pancreatic cancer has a relatively abundant fibrous stroma and sparse tumor vascularity, which translates to a low signal intensity on noncontrast T1-weighted fat-suppressed images and less enhancement than the surrounding normal pancreatic tissue on immediate postcontrast images (100) (Fig 5). Recently reported values for the sensitivity and specificity of MR imaging for the diagnosis of pancreatic cancer in single

center studies are 85%–93% and 72%–79%, respectively (101,102).

In addition to routine multiplanar MR studies, MRCP can be used to noninvasively characterize the biliary and pancreatic ducts. MRCP utilizes heavily T2-weighted sequences to show the signal of static or slow-moving fluid-filled structures. Studies have demonstrated that MRCP is comparable to the more invasive ERCP for the diagnosis of pancreatic tumors that involve the main pancreatic duct (103,104). However, the precancerous lesions, such as PIN grade 3, which can cause narrowing, blebbing, or ectatic side-branches, can be more difficult to assess with MRCP.

Figure 5: Images acquired with a 1.5-T imager in 70-year-old man with pancreatic head ductal adenocarcinoma. **(a)** Fat-suppressed T1-weighted postcontrast image (repetition time msec/echo time msec, 2.9/1.3) shows a 2.3×2.0 -cm mass (arrow) in the head of the pancreas. Note that the mass is hypoenhancing relative to the normal surrounding pancreatic parenchyma (arrowhead). **(b)** Coronal T2-weighted MRCP image (815/180) shows a T2 hyperintense obstructing mass (arrow) in the head of the pancreas with associated dilation of the main pancreatic duct (arrowhead) and atrophy of the body and tail of the pancreas. **(c)** Diffusion-weighted image (11.3/59.9) and **(d)** apparent diffusion coefficient map confirm that the mass (arrow) is associated with restricted diffusion.

Although ERCP has served as the reference standard, the advantage of MRCP over endoscopic US is that it can be combined with routine multiplanar MR of the upper abdomen to evaluate not only the pancreatic and biliary ducts, but also the liver.

Diffusion-weighted MR Imaging

Diffusion is caused by random molecular motion, also known as Brownian motion (105). Diffusion-weighted (DW) MR imaging is the only imaging method that can be used to evaluate the diffusion process in vivo. DW imaging is increasingly being used within the abdomen (106,107). Various malignant tumors demonstrate high-signal-intensity on DW images, likely reflecting high cellularity and/or a long T2 relaxation time (108). Several investigators have used DW imaging to detect PDAC. Muraoka et al (109) reported that the apparent diffusion coefficient (ADC) in PDAC correlates with tumor fibrosis rather than with tumor cellularity. Ichikawa et al reported a very high sensitivity (96.2%) and specificity (98.6%) for detecting PDAC using DW imaging only (106). More recent studies have reported that pancreatic cancer exhibits a high signal intensity on DW images with a significantly decreased ADC value compared with that of normal parenchyma (107,110) (Fig 5). ADC has also proven helpful for differentiating between pancreatic cancer and mass-forming focal pancreatitis (111,112). While the results of these studies indicate that DW imaging may be useful for characterizing pancreatic lesions, it has yet to be shown that DW imaging can help detect pancreatic cancer at an earlier stage. It is also unclear how much diagnostic accuracy is improved, if at all, when DW imaging is added to MR protocols for PDAC. Kartalis et al found similar diagnostic accuracy for pancreatic cancer when comparing their conventional MR protocol to the same MR protocol with DW imaging added (113).

MR Spectroscopy

MR spectroscopy provides a noninvasive measurement of biochemical information in vivo (114). Several

investigators have described the use of MR spectroscopy to characterize pancreatic neoplasms. Cho et al found less lipid in chronic focal pancreatitis than in PDAC, with a sensitivity and specificity of 100% and 53.3%, respectively, for differentiating pancreatic cancer from focal pancreatitis (115). Ma et al used MR spectroscopy at 3 T to compare the metabolic features of PDAC with that of normal pancreas in control subjects (116). When compared with normal pancreas, choline-containing compounds, fatty acids, and lipids were all decreased in PDAC. The authors hypothesized that the hypoperfusion and hypometabolism of PDAC relative to the surrounding pancreatic parenchyma contribute to these changes. MR spectroscopy is a promising method for improving the sensitivity, but not the specificity, for the diagnosis of PDAC. However, metabolic molecular information is currently limited by the relatively low magnetic field and signal strength associated with MR spectroscopy for clinic use.

Potential Improvements of MR Imaging with Molecularly Targeted Contrast Agents

MR imaging is associated with excellent soft-tissue contrast, but low sensitivity, which makes the development of molecular probes more challenging compared with other modalities such as positron emission tomography (PET, discussed below), US, and optical imaging. Contrast agents based on nanoparticulate probes with a high payload of contrast-generating metals have been developed to overcome the low sensitivity associated with MR imaging. Tumor-targeted MR imaging has been performed by using gadolinium (III)-containing micelles and liposomes, superparamagnetic iron oxide nanoparticles, and manganese (II) chelates (88,89,117–120). At present, superparamagnetic iron oxide nanoparticles are the most attractive due to their chemical stability and biocompatibility, with an overall hydrodynamic diameter of less than 50 nm, much smaller than a cell (normally 10–30 μ m) (120). Studies on MR imaging–targeting biomarkers

such as plectin-1 or epidermal growth factor receptor, which are overexpressed in pancreatic cancer, have been published. Targeted contrast agents were developed by attaching peptide or single-chain antibodies to iron oxide nanoparticles and imaged (121,122). Results of these studies using tissue specimens and subcutaneously implanted tumors in animal models (Fig 6) demonstrated the feasibility of using targeted nanoparticle probes for both ex vivo and in vivo MR imaging. Molecular MR imaging for earlier detection of PDAC has not yet been translated into clinical trials.

The role of MR imaging for the early detection of pancreatic cancer continues to evolve. MR imaging is particularly attractive as a screening modality because it does not rely on ionizing radiation and can be used for patients with an allergy to iodinated contrast material. Moreover, MR imaging is associated with excellent soft-tissue contrast and the ability to evaluate the ducts with use of MRCP. Despite these advantages and a comparable diagnostic accuracy for staging pancreatic cancer, multidetector CT continues to be more widely used than MR imaging for diagnosing and staging pancreatic cancer. Greater adoption of MR imaging is likely limited by the higher spatial resolution, lower cost, and greater availability of multidetector CT.

FDG PET

Elevated uptake of 18 fluorine (18 F) fluorodeoxyglucose (FDG) has been demonstrated in most primary malignant tumors because of increased metabolism of glucose (123). Early studies demonstrated quantitative and selective overexpression of GLUT-1 transporters in malignant pancreatic lesions (124), while normal pancreatic tissue has low glucose utilization. Studies have demonstrated that FDG PET has a relatively high sensitivity (88%–94%) but variable specificity (60%–94%) for differentiating benign from malignant pancreatic masses (125–130). Compared with CT and MR imaging, FDG PET is more sensitive for detection of small pancreatic tumors (131,132) and

Figure 6

b.

Figure 6: In vivo MR imaging with epidermal growth factor receptor (EGFR)-targeted iron oxide nanoparticles using an orthotopic human pancreatic cancer xenograft model. **(a)** Pre- and postcontrast T2-weighted fast spin-echo images at 5 and 30 hours after injection of single-chain anti-EGFR antibody (ScFvEGFR) conjugated to magnetic iron oxide nanoparticles show selective accumulation of the nanoparticles within the pancreatic tumors, as evidenced by a decrease in signal within the tumor (dash-lined pink circle). Upper and lower panels show different levels from the same mouse. Signal changes were also noted in liver (green arrow) and spleen. Lower right image shows the corresponding gross specimen with the intrapancreatic tumors (blue arrows). **(b)** MR images from a mouse that received nontargeted control iron oxide nanoparticles did not show detectable signal changes at similar time points. Lower right image shows the corresponding gross specimen within the tumor (blue arrow). (Adapted and reprinted, with permission, from reference 122.)

recurrent pancreatic cancer (133,134). However, PET has been associated with a high rate of false-positive results,

particularly in patients with mass-forming pancreatitis (135). With the development and combination of PET

and CT, the ability of FDG imaging to provide accurate anatomic localization has been improved greatly (Fig 7). Several articles (136,137) have reported a higher sensitivity, but not specificity, of PET/CT for detection of pancreatic cancer when compared with CT or PET alone. In a recent meta-analysis comparing FDG PET, combined FDG PET/CT, and endoscopic US for diagnosing primary pancreatic carcinoma, the pooled sensitivity for PET/CT was higher than that of PET and endoscopic US, while the pooled specificity estimate for endoscopic US was higher than that for PET and PET/CT (136). Currently, the relatively low specificity, high cost, somewhat limited availability, and ionizing radiation all limit the use of PET or PET/CT as a first-line diagnostic tool for pancreatic cancer. PET/CT can help establish the diagnosis of pancreatic carcinoma in patients suspected of having pancreatic cancer in whom CT fails to identify a discrete tumor mass or in whom fine needle aspirations are non-diagnostic (137).

Improving Sensitivity and Specificity of PET with New Radiotracers

Carbon 11 (^{11}C)-acetate PET, which is thought to be metabolized by entering the lipid synthesis pathway (138), may also be useful for malignant tumor diagnosis. As the cellular uptake of acetate is not affected by glucose metabolism, ^{11}C -acetate PET may provide superior detectability over FDG PET for malignancy and is expected to be equally effective even in hyperglycemic states. In a recent study, Zhao et al (139) reported earlier detection of pancreatic cancer xenografts with ^{11}C -acetate PET than with FDG PET, but the ratio of radiotracer accumulation between tumor and nontumor in ^{11}C -acetate PET was lower than that in FDG PET during the same period. Another radiotracer, ^{18}F -FEDL, which is overexpressed in peritumoral pancreatic acinar cells, was reported to be helpful for detection of small pancreatic cancer lesions (140). Additional studies are needed to evaluate the performance of new radiotracers for detecting and characterizing pancreatic cancer specifically.

Figure 7: Images in 56-year-old man with biopsy-proven ductal adenocarcinoma of the pancreatic tail. **(a)** Low-dose noncontrast CT image acquired for attenuation correction and anatomic localization shows focal prominence of the pancreatic tail (arrow) suggestive of an underlying mass. **(b)** Fused, attenuation-corrected FDG PET-CT image demonstrates focal uptake of FDG (arrow) in the pancreatic tail.

With recent advances in nanoparticle engineering, radiolabeled antibody or gene-based probes have been developed that target specific proteins or genes overexpressed on the surface or inside tumor cells (or vascular endothelial cells). These targeted probes promise to increase diagnostic specificity. For example, the epithelial cell surface receptor $\alpha\beta6$ is overexpressed in many different cancers, including pancreatic, cervical, lung, and colon cancers. Hausner et al (141) have shown the feasibility of imaging $\alpha\beta6$ in vivo by using PET and a new radiotracer, [^{18}F]FBA-A20FMDV2 and its improved format [^{18}F]FBA-PEG28-A20FMDV2. With the new compounds, they were able to achieve excellent tumor retention and good clearance of non-specifically bound tracer resulting in tumor-pancreas biodistribution ratios of greater than 23:1 in a mouse model of pancreatic carcinoma. Kimura et al have also successfully targeted integrin $\alpha\beta6$ using pancreatic and epidermoid cancer xenografts or orthotopic models (142). They engineered peptides with a high affinity and specificity for integrin $\alpha\beta6$, but no cross-reactivity to related integrins. Uptake of the radiotracers by integrin $\alpha\beta6$ -expressing tumors was rapid and high, and off-target background was minimized.

Finally, given that 95% of patients with ductal pancreatic cancer carry 12th codon activating mutations in their *KRAS2* oncogenes, attempts have been made to image mutant *KRAS2* mRNA activation by using PET and mutant *KRAS2* peptide nucleic acid (143,144). By using *IGF1R* (insulin-like growth factor 1)-overexpressing AsPC-1 pancreas cancer xenografts in immunocompromised mice, a [(64)Cu]KRAS-IGF1 radiohybridization probe resulted in improved tumor contrast on PET images, with an 8.6-fold increase in signal intensity within the human pancreas cancer xenografts when compared with the contralateral muscle.

Challenges Translating New Molecularly Targeted Contrast Agents into the Clinic

It is expected that ongoing complementary research on new biomarker and imaging-based approaches will result in earlier detection of pancreatic cancer in the future. However, one of the challenges in developing new molecular imaging-based approaches with novel contrast agents is the inability to fail quickly and early during the contrast agent development process, in particular during the costly phases of clinical testing. Ideally, once a new contrast agent has shown to be safe and effective in preclinical studies, the

agent should be quickly tested in pilot clinical trials to assess its efficacy in patients. If the agent continues to show promise in the clinical setting, its development could be expedited, whereas its development could be halted immediately in case of disappointing results. This recognition of quick and early failure would give researchers the opportunity to save resources and concentrate their efforts on the most promising contrast agent candidates to be moved through the different phases of clinical trials. However, since molecular imaging agents are treated as drugs by the FDA, they must undergo the same lengthy approval process as any other drug. This does not allow for quick go or no-go decisions for many contrast agents. Fortunately, for PET agents that are injected in trace amounts (defined as $\leq 100 \mu\text{g}$ for imaging agents and 30 nmol for protein products), an exploratory investigative new drug application (IND) pathway had been introduced by the FDA, allowing translation into early first-in-human phase 0 clinical trials, with less requirements for preclinical animal testing than is typically needed for a traditional IND (88). Researchers from the Crump Institute for Molecular imaging at the University of California Los Angeles recently reported on a

streamlined and cost-effective pipeline at their institution to obtain traditional IND approvals from the FDA to allow timely clinical translation of new PET agents (145). Through their pipeline, a traditional IND for a PET probe can be obtained within 7 months at a cost of approximately \$50 000, if safety and toxicity assessment are obtained for several agents conjointly and by using their own intramural nonprofit free-for-service facilities. These costs, however, were estimated at \$150 000 per agent using contract research organizations (145). There is less experience in clinical translation for molecularly targeted contrast agents other than PET agents. However, this example shows that, through a team effort, the FDA approval process for molecular contrast agents can be expedited. It is expected that similar pipelines could be developed for other types of contrast agents in the future. For example, a first molecularly targeted US contrast agent has been recently moved into a first clinical trial in the United States following FDA IND approval (*clinicaltrials.gov*, no. NCT02142608), and the experience from this process could be leveraged to expedite translating similar or next-generation US contrast agents into the clinic.

Conclusion

Pancreatic cancer is a deadly disease with a dismal prognosis, particularly when diagnosed at a later stage. Currently, there is no suitable screening strategy available for the general population. Efforts to detect PDAC at earlier stages have largely focused on high-risk cohorts that comprise approximately 10% of all patients with PDAC and include a combination of endoscopic US, MRCP, and, in some centers, ERCP for very high-risk patients. The cost and invasive nature of these imaging tests prevents this strategy from being used in moderate-risk individuals (patients with adult-onset diabetes) and for the general population. Many novel molecular and targeting imaging agents are being developed in an effort to improve the specificity of the imaging modalities

discussed above. While many of these probes are early in development, results of preliminary studies are promising and suggest that these approaches, in combination with biomarkers, will potentially lead to improved screening and early detection of PDAC in the future.

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References

- Hruban RH, Pitman MB, Klimstra DS. Tumors of the pancreas. Washington, DC: American Registry of Pathology, 2007.
- Korc M. Pancreatic cancer-associated stroma production. *Am J Surg* 2007;194(4, Suppl):S84-S86.
- Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin* 2012;62(1):10-29.
- Wagner M, Redaelli C, Lietz M, Seiler CA, Friess H, Büchler MW. Curative resection is the single most important factor determining outcome in patients with pancreatic adenocarcinoma. *Br J Surg* 2004;91(5):586-594.
- Lowenfels AB, Sullivan T, Fiorianti J, Maisonneuve P. The epidemiology and impact of pancreatic diseases in the United States. *Curr Gastroenterol Rep* 2005;7(2):90-95.
- Wang YY, Cui QC. Recent advances in gene change of pancreatic cancer [in Chinese]. *Zhongguo Yi Xue Ke Xue Yuan Xue Bao* 2004;26(1):79-82.
- Jones S, Zhang X, Parsons DW, et al. Core signaling pathways in human pancreatic cancers revealed by global genomic analyses. *Science* 2008;321(5897):1801-1806.
- Bausch D, Thomas S, Mino-Kenudson M, et al. Plectin-1 as a novel biomarker for pancreatic cancer. *Clin Cancer Res* 2011;17(2):302-309.
- Seo Y, Baba H, Fukuda T, Takashima M, Sugimachi K. High expression of vascular endothelial growth factor is associated with liver metastasis and a poor prognosis for patients with ductal pancreatic adenocarcinoma. *Cancer* 2000;88(10):2239-2245.
- Lynch HT, Smyrk T, Kern SE, et al. Familial pancreatic cancer: a review. *Semin Oncol* 1996;23(2):251-275.
- Shi C, Hruban RH, Klein AP. Familial pancreatic cancer. *Arch Pathol Lab Med* 2009;133(3):365-374.
- Hruban RH, Canto MI, Goggins M, Schlick R, Klein AP. Update on familial pancreatic cancer. *Adv Surg* 2010;44:293-311.
- Klein AP, Brune KA, Petersen GM, et al. Prospective risk of pancreatic cancer in familial pancreatic cancer kindreds. *Cancer Res* 2004;64(7):2634-2638.
- Chari ST, Leibson CL, Rabe KG, et al. Pancreatic cancer-associated diabetes mellitus: prevalence and temporal association with diagnosis of cancer. *Gastroenterology* 2008;134(1):95-101.
- Pannala R, Basu A, Petersen GM, Chari ST. New-onset diabetes: a potential clue to the early diagnosis of pancreatic cancer. *Lancet Oncol* 2009;10(1):88-95.
- Liao WC, Chien KL, Lin YL, et al. Adjuvant treatments for resected pancreatic adenocarcinoma: a systematic review and network meta-analysis. *Lancet Oncol* 2013;14(11):1095-1103.
- Winter JM, Cameron JL, Campbell KA, et al. 1423 pancreaticoduodenectomies for pancreatic cancer: a single-institution experience. *J Gastrointest Surg* 2006;10(9):1199-1210; discussion 1210-1211.
- Zhang JF, Hua R, Sun YW, et al. Influence of perineural invasion on survival and recurrence in patients with resected pancreatic cancer. *Asian Pac J Cancer Prev* 2013;14(9):5133-5139.
- Chatterjee D, Katz MH, Rashid A, et al. Perineural and intraneural invasion in post-therapy pancreaticoduodenectomy specimens predicts poor prognosis in patients with pancreatic ductal adenocarcinoma. *Am J Surg Pathol* 2012;36(3):409-417.
- Hermanek P. Pathology and biology of pancreatic ductal adenocarcinoma. *Langenbecks Arch Surg* 1998;383(2):116-120.
- Liu H, Li X, Xu Q, Lv S, Li J, Ma Q. Role of glial cell line-derived neurotrophic factor in perineural invasion of pancreatic cancer. *Biochim Biophys Acta* 2012;1826(1):112-120.
- Furukawa H, Okada S, Saisho H, et al. Clinicopathologic features of small pancreatic adenocarcinoma: a collective study. *Cancer* 1996;78(5):986-990.
- Gemmel C, Eickhoff A, Helmstädter L, Riemann JF. Pancreatic cancer screening: state of the art. *Expert Rev Gastroenterol Hepatol* 2009;3(1):89-96.

24. Helmstaedter L, Riemann JF. Pancreatic cancer: EUS and early diagnosis. *Langenbecks Arch Surg* 2008;393(6):923–927.
25. Pandharipande PV, Heberle C, Dowling EC, et al. Targeted screening of individuals at high risk for pancreatic cancer: results of a simulation model. *Radiology* 2015;275(1):177–187.
26. Brentnall TA, Bronner MP, Byrd DR, Haggitt RC, Kimmey MB. Early diagnosis and treatment of pancreatic dysplasia in patients with a family history of pancreatic cancer. *Ann Intern Med* 1999;131(4):247–255.
27. Rulyak SJ, Kimmey MB, Veenstra DL, Brentnall TA. Cost-effectiveness of pancreatic cancer screening in familial pancreatic cancer kindreds. *Gastrointest Endosc* 2003;57(1):23–29.
28. Brentnall TA. Pancreatic cancer surveillance: learning as we go. *Am J Gastroenterol* 2011;106(5):955–956.
29. Brand RE, Lerch MM, Rubinstein WS, et al. Advances in counselling and surveillance of patients at risk for pancreatic cancer. *Gut* 2007;56(10):1460–1469.
30. Templeton AW, Brentnall TA. Screening and surgical outcomes of familial pancreatic cancer. *Surg Clin North Am* 2013;93(3):629–645.
31. Winter JM, Yeo CJ, Brody JR. Diagnostic, prognostic, and predictive biomarkers in pancreatic cancer. *J Surg Oncol* 2013;107(1):15–22.
32. Brand RE, Nolen BM, Zeh HJ, et al. Serum biomarker panels for the detection of pancreatic cancer. *Clin Cancer Res* 2011;17(4):805–816.
33. Kim JE, Lee KT, Lee JK, Paik SW, Rhee JC, Choi KW. Clinical usefulness of carbohydrate antigen 19-9 as a screening test for pancreatic cancer in an asymptomatic population. *J Gastroenterol Hepatol* 2004;19(2):182–186.
34. Duraker N, Hot S, Polat Y, Höbek A, Gengler N, Urhan N. CEA, CA 19-9, and CA 125 in the differential diagnosis of benign and malignant pancreatic diseases with or without jaundice. *J Surg Oncol* 2007;95(2):142–147.
35. Olsen TS. The incidence and clinical relevance of chronic inflammation in the pancreas in autopsy material. *Acta Pathol Microbiol Scand [A]* 1978;86A(5):361–365.
36. Shimizu M, Hayashi T, Saitoh Y, Itoh H. Interstitial fibrosis in the pancreas. *Am J Clin Pathol* 1989;91(5):531–534.
37. Stamm BH. Incidence and diagnostic significance of minor pathologic changes in the adult pancreas at autopsy: a systematic study of 112 autopsies in patients without known pancreatic disease. *Hum Pathol* 1984;15(7):677–683.
38. Pan S, Chen R, Brand RE, et al. Multiplex targeted proteomic assay for biomarker detection in plasma: a pancreatic cancer biomarker case study. *J Proteome Res* 2012;11(3):1937–1948.
39. Pan S, Chen R, Crispin DA, et al. Protein alterations associated with pancreatic cancer and chronic pancreatitis found in human plasma using global quantitative proteomics profiling. *J Proteome Res* 2011;10(5):2359–2376.
40. Kawaguchi T, Komatsu S, Ichikawa D, et al. Clinical impact of circulating miR-221 in plasma of patients with pancreatic cancer. *Br J Cancer* 2013;108(2):361–369.
41. Wang J, Chen J, Chang P, et al. MicroRNAs in plasma of pancreatic ductal adenocarcinoma patients as novel blood-based biomarkers of disease. *Cancer Prev Res (Phila)* 2009;2(9):807–813.
42. Zhang L, Farrell JJ, Zhou H, et al. Salivary transcriptomic biomarkers for detection of resectable pancreatic cancer. *Gastroenterology* 2010;138(3):949–57.e1–e7.
43. Park JK, Ryu JK, Yoon WJ, et al. The role of quantitative NPTX2 hypermethylation as a novel serum diagnostic marker in pancreatic cancer. *Pancreas* 2012;41(1):95–101.
44. Liggett T, Melnikov A, Yi QL, et al. Differential methylation of cell-free circulating DNA among patients with pancreatic cancer versus chronic pancreatitis. *Cancer* 2010;116(7):1674–1680.
45. Farrell JJ, Zhang L, Zhou H, et al. Variations of oral microbiota are associated with pancreatic diseases including pancreatic cancer. *Gut* 2012;61(4):582–588.
46. Kersting S, Konopke R, Kersting F, et al. Quantitative perfusion analysis of transabdominal contrast-enhanced ultrasonography of pancreatic masses and carcinomas. *Gastroenterology* 2009;137(6):1903–1911.
47. Balci NC, Semelka RC. Radiologic diagnosis and staging of pancreatic ductal adenocarcinoma. *Eur J Radiol* 2001;38(2):105–112.
48. Hua YP, Liang LJ, Peng BG, Li SQ, Huang JF. Pancreatic head carcinoma: clinical analysis of 189 cases. *Hepatobiliary Pancreat Dis Int* 2009;8(1):79–84.
49. Lencioni R, Cioni D, Bartolozzi C. Tissue harmonic and contrast-specific imaging: back to gray scale in ultrasound. *Eur Radiol* 2002;12(1):151–165.
50. Okamoto Y, Kawamoto H, Takaki A, et al. Contrast-enhanced ultrasonography depicts small tumor vessels for the evaluation of pancreatic tumors. *Eur J Radiol* 2007;61(1):163–169.
51. Takeda K, Goto H, Hirooka Y, et al. Contrast-enhanced transabdominal ultrasonography in the diagnosis of pancreatic mass lesions. *Acta Radiol* 2003;44(1):103–106.
52. Dietrich CF, Braden B, Hocke M, Ott M, Ignee A. Improved characterisation of solitary solid pancreatic tumours using contrast enhanced transabdominal ultrasound. *J Cancer Res Clin Oncol* 2008;134(6):635–643.
53. Shapiro RS, Wagreich J, Parsons RB, Stancato-Pasik A, Yeh HC, Lao R. Tissue harmonic imaging sonography: evaluation of image quality compared with conventional sonography. *AJR Am J Roentgenol* 1998;171(5):1203–1206.
54. Sofuni A, Iijima H, Moriyasu F, et al. Differential diagnosis of pancreatic tumors using ultrasound contrast imaging. *J Gastroenterol* 2005;40(5):518–525.
55. D'Onofrio M, Malagò R, Zamboni G, et al. Contrast-enhanced ultrasonography better identifies pancreatic tumor vascularization than helical CT. *Pancreatol* 2005;5(4-5):398–402.
56. D'Onofrio M, Zamboni G, Tognolini A, et al. Mass-forming pancreatitis: value of contrast-enhanced ultrasonography. *World J Gastroenterol* 2006;12(26):4181–4184.
57. Canto MI, Goggins M, Yeo CJ, et al. Screening for pancreatic neoplasia in high-risk individuals: an EUS-based approach. *Clin Gastroenterol Hepatol* 2004;2(7):606–621.
58. Lee MX, Saif MW. Screening for early pancreatic ductal adenocarcinoma: an urgent call! *JOP* 2009;10(2):104–108.
59. Ahmad NA, Kochman ML, Brensinger C, et al. Interobserver agreement among endosonographers for the diagnosis of neoplastic versus non-neoplastic pancreatic cystic lesions. *Gastrointest Endosc* 2003;58(1):59–64.
60. Topazian M, Enders F, Kimmey M, et al. Interobserver agreement for EUS findings in familial pancreatic-cancer kindreds. *Gastrointest Endosc* 2007;66(1):62–67.
61. Pysz MA, Willmann JK. Targeted contrast-enhanced ultrasound: an emerging technology in abdominal and pelvic imaging. *Gastroenterology* 2011;140(3):785–790.
62. Wilson KE, Wang TY, Willmann JK. Acoustic and photoacoustic molecular imaging of cancer. *J Nucl Med* 2013;54(11):1851–1854.

63. Pysz MA, Machtaler SB, Seeley ES, et al. Vascular endothelial growth factor receptor type 2-targeted contrast-enhanced US of pancreatic cancer neovasculature in a genetically engineered mouse model: potential for earlier detection. *Radiology* 2015; 274(3):790–799.
64. Bachawal SV, Jensen KC, Lutz AM, et al. Earlier detection of breast cancer with ultrasound molecular imaging in a transgenic mouse model. *Cancer Res* 2013;73(6):1689–1698.
65. Lee DJ, Lyshchik A, Huamani J, Hallahan DE, Fleischer AC. Relationship between retention of a vascular endothelial growth factor receptor 2 (VEGFR2)-targeted ultrasonographic contrast agent and the level of VEGFR2 expression in an in vivo breast cancer model. *J Ultrasound Med* 2008;27(6):855–866.
66. Rychak JJ, Graba J, Cheung AMY, et al. Microultrasound molecular imaging of vascular endothelial growth factor receptor 2 in a mouse model of tumor angiogenesis. *Mol Imaging* 2007;6(5):289–296.
67. Pysz MA, Foygel K, Rosenberg J, Gambhir SS, Schneider M, Willmann JK. Antiangiogenic cancer therapy: monitoring with molecular US and a clinically translatable contrast agent (BR55). *Radiology* 2010; 256(2):519–527.
68. Korpanty G, Carbon JG, Grayburn PA, Fleming JB, Brekken RA. Monitoring response to anticancer therapy by targeting microbubbles to tumor vasculature. *Clin Cancer Res* 2007;13(1):323–330.
69. Pochon S, Tardy I, Bussat P, et al. BR55: a lipopeptide-based VEGFR2-targeted ultrasound contrast agent for molecular imaging of angiogenesis. *Invest Radiol* 2010;45(2):89–95.
70. Tardy I, Pochon S, Theraulaz M, et al. Ultrasound molecular imaging of VEGFR2 in a rat prostate tumor model using BR55. *Invest Radiol* 2010;45(10):573–578.
71. Foygel K, Wang H, Machtaler S, et al. Detection of pancreatic ductal adenocarcinoma in mice by ultrasound imaging of thymocyte differentiation antigen 1. *Gastroenterology* 2013;145(4):885–894.e3.
72. Kaneko OF, Willmann JK. Ultrasound for molecular imaging and therapy in cancer. *Quant Imaging Med Surg* 2012;2(2):87–97.
73. Kim JH, Park SH, Yu ES, et al. Visually isoattenuating pancreatic adenocarcinoma at dynamic-enhanced CT: frequency, clinical and pathologic characteristics, and diagnosis at imaging examinations. *Radiology* 2010;257(1):87–96.
74. Ahn SS, Kim MJ, Choi JY, Hong HS, Chung YE, Lim JS. Indicative findings of pancreatic cancer in prediagnostic CT. *Eur Radiol* 2009;19(10):2448–2455.
75. Peddu P, Quaglia A, Kane PA, Karani JB. Role of imaging in the management of pancreatic mass. *Crit Rev Oncol Hematol* 2009;70(1):12–23.
76. Lu DS, Vedantham S, Krasny RM, Kadell B, Berger WL, Reber HA. Two-phase helical CT for pancreatic tumors: pancreatic versus hepatic phase enhancement of tumor, pancreas, and vascular structures. *Radiology* 1996;199(3):697–701.
77. Valls C, Andía E, Sanchez A, et al. Dual-phase helical CT of pancreatic adenocarcinoma: assessment of resectability before surgery. *AJR Am J Roentgenol* 2002;178(4):821–826.
78. Kaneko OF, Lee DM, Wong J, et al. Performance of multidetector computed tomographic angiography in determining surgical resectability of pancreatic head adenocarcinoma. *J Comput Assist Tomogr* 2010;34(5):732–738.
79. Kim SH, Kamaya A, Willmann JK. CT perfusion of the liver: principles and applications in oncology. *Radiology* 2014;272(2):322–344.
80. Klaus M, Stiller W, Fritz F, et al. Computed tomography perfusion analysis of pancreatic carcinoma. *J Comput Assist Tomogr* 2012;36(2):237–242.
81. Delrue L, Blanckaert P, Mertens D, Cessmel E, Ceelen WP, Duyck P. Assessment of tumor vascularization in pancreatic adenocarcinoma using 128-slice perfusion computed tomography imaging. *J Comput Assist Tomogr* 2011;35(4):434–438.
82. Lu N, Feng XY, Hao SJ, et al. 64-slice CT perfusion imaging of pancreatic adenocarcinoma and mass-forming chronic pancreatitis. *Acad Radiol* 2011;18(1):81–88.
83. Kandel S, Kloeters C, Meyer H, Hein P, Hilbig A, Rogalla P. Whole-organ perfusion of the pancreas using dynamic volume CT in patients with primary pancreas carcinoma: acquisition technique, post-processing and initial results. *Eur Radiol* 2009;19(11):2641–2646.
84. Xu J, Liang Z, Hao S, et al. Pancreatic adenocarcinoma: dynamic 64-slice helical CT with perfusion imaging. *Abdom Imaging* 2009;34(6):759–766.
85. Patel BN, Thomas JV, Lockhart ME, Berland LL, Morgan DE. Single-source dual-energy spectral multidetector CT of pancreatic adenocarcinoma: optimization of energy level viewing significantly increases lesion contrast. *Clin Radiol* 2013;68(2):148–154.
86. Montet X, Pastor CM, Vallée JP, et al. Improved visualization of vessels and hepatic tumors by micro-computed tomography (CT) using iodinated liposomes. *Invest Radiol* 2007;42(9):652–658.
87. Mukundan S Jr, Ghaghada KB, Badea CT, et al. A liposomal nanoscale contrast agent for preclinical CT in mice. *AJR Am J Roentgenol* 2006;186(2):300–307.
88. Kircher MF, Willmann JK. Molecular body imaging: MR imaging, CT, and US. II. Applications. *Radiology* 2012;264(2):349–368.
89. Kircher MF, Willmann JK. Molecular body imaging: MR imaging, CT, and US. I. Principles. *Radiology* 2012;263(3):633–643.
90. Danila D, Partha R, Elrod DB, Lackey M, Casscells SW, Conyers JL. Antibody-labeled liposomes for CT imaging of atherosclerotic plaques: in vitro investigation of an anti-ICAM antibody-labeled liposome containing iohexol for molecular imaging of atherosclerotic plaques via computed tomography. *Tex Heart Inst J* 2009;36(5):393–403.
91. Wyss C, Schaefer SC, Juillerat-Jeanneret L, et al. Molecular imaging by micro-CT: specific E-selectin imaging. *Eur Radiol* 2009;19(10):2487–2494.
92. Martens CL, Cwirla SE, Lee RY, et al. Peptides which bind to E-selectin and block neutrophil adhesion. *J Biol Chem* 1995;270(36):21129–21136.
93. Bischoff J, Brasel C, Kräling B, Vranovska K. E-selectin is upregulated in proliferating endothelial cells in vitro. *Microcirculation* 1997;4(2):279–287.
94. Willmann JK, van Bruggen N, Dinkelborg LM, Gambhir SS. Molecular imaging in drug development. *Nat Rev Drug Discov* 2008; 7(7):591–607.
95. Gilinsky NH, Bornman PC, Girdwood AH, Marks IN. Diagnostic yield of endoscopic retrograde cholangiopancreatography in carcinoma of the pancreas. *Br J Surg* 1986;73(7):539–543.
96. Menges M, Lerch MM, Zeitz M. The double duct sign in patients with malignant and benign pancreatic lesions. *Gastrointest Endosc* 2000;52(1):74–77.
97. Vachiranubhapp B, Kim YH, Balci NC, Semelka RC. Magnetic resonance imaging of adenocarcinoma of the pancreas. *Top Magn Reson Imaging* 2009;20(1):3–9.

98. Kim JK, Altun E, Elias J Jr, Pamuklar E, Rivero H, Semelka RC. Focal pancreatic mass: distinction of pancreatic cancer from chronic pancreatitis using gadolinium-enhanced 3D-gradient-echo MRI. *J Magn Reson Imaging* 2007;26(2):313–322.
99. Schima W, Ba-Ssalamah A, Goetzinger P, Scharitzer M, Koelblinger C. State-of-the-art magnetic resonance imaging of pancreatic cancer. *Top Magn Reson Imaging* 2007;18(6):421–429.
100. Kelekis NL, Semelka RC. MRI of pancreatic tumors. *Eur Radiol* 1997;7(6):875–886.
101. Kauhanen SP, Komar G, Seppänen MP, et al. A prospective diagnostic accuracy study of 18F-fluorodeoxyglucose positron emission tomography/computed tomography, multidetector row computed tomography, and magnetic resonance imaging in primary diagnosis and staging of pancreatic cancer. *Ann Surg* 2009;250(6):957–963.
102. Bipat S, Phoa SS, van Delden OM, et al. Ultrasonography, computed tomography and magnetic resonance imaging for diagnosis and determining resectability of pancreatic adenocarcinoma: a meta-analysis. *J Comput Assist Tomogr* 2005;29(4):438–445.
103. Hekimoglu K, Ustundag Y, Dusak A, et al. MRCP vs ERCP in the evaluation of biliary pathologies: review of current literature. *J Dig Dis* 2008;9(3):162–169.
104. Adamek HE, Albert J, Breer H, Weitz M, Schilling D, Riemann JF. Pancreatic cancer detection with magnetic resonance cholangiopancreatography and endoscopic retrograde cholangiopancreatography: a prospective controlled study. *Lancet* 2000;356(9225):190–193.
105. Dzik-Jurasz A, Domenig C, George M, et al. Diffusion MRI for prediction of response of rectal cancer to chemoradiation. *Lancet* 2002;360(9329):307–308.
106. Ichikawa T, Erturk SM, Motosugi U, et al. High-b value diffusion-weighted MRI for detecting pancreatic adenocarcinoma: preliminary results. *AJR Am J Roentgenol* 2007;188(2):409–414.
107. Matsuki M, Inada Y, Nakai G, et al. Diffusion-weighted MR imaging of pancreatic carcinoma. *Abdom Imaging* 2007;32(4):481–483.
108. Nasu K, Kuroki Y, Nawano S, et al. Hepatic metastases: diffusion-weighted sensitivity-encoding versus SPIO-enhanced MR imaging. *Radiology* 2006;239(1):122–130.
109. Muraoka N, Uematsu H, Kimura H, et al. Apparent diffusion coefficient in pancreatic cancer: characterization and histopathological correlations. *J Magn Reson Imaging* 2008;27(6):1302–1308.
110. Lemke A, Laun FB, Klauss M, et al. Differentiation of pancreas carcinoma from healthy pancreatic tissue using multiple b-values: comparison of apparent diffusion coefficient and intravoxel incoherent motion derived parameters. *Invest Radiol* 2009;44(12):769–775.
111. Takeuchi M, Matsuzaki K, Kubo H, Nishitani H. High-b-value diffusion-weighted magnetic resonance imaging of pancreatic cancer and mass-forming chronic pancreatitis: preliminary results. *Acta Radiol* 2008;49(4):383–386.
112. Fattahi R, Balci NC, Perman WH, et al. Pancreatic diffusion-weighted imaging (DWI): comparison between mass-forming focal pancreatitis (FP), pancreatic cancer (PC), and normal pancreas. *J Magn Reson Imaging* 2009;29(2):350–356.
113. Kartalis N, Lindholm TL, Aspelin P, Permert J, Albiin N. Diffusion-weighted magnetic resonance imaging of pancreas tumours. *Eur Radiol* 2009;19(8):1981–1990.
114. Henriksen O. MR spectroscopy in clinical research. *Acta Radiol* 1994;35(2):96–116.
115. Cho SG, Lee DH, Lee KY, et al. Differentiation of chronic focal pancreatitis from pancreatic carcinoma by in vivo proton magnetic resonance spectroscopy. *J Comput Assist Tomogr* 2005;29(2):163–169.
116. Ma X, Zhao X, Ouyang H, et al. The metabolic features of normal pancreas and pancreatic adenocarcinoma: preliminary result of in vivo proton magnetic resonance spectroscopy at 3.0 T. *J Comput Assist Tomogr* 2011;35(5):539–543.
117. Kozłowska D, Foran P, MacMahon P, Shelly MJ, Eustace S, O'Kennedy R. Molecular and magnetic resonance imaging: the value of immunoliposomes. *Adv Drug Deliv Rev* 2009;61(15):1402–1411.
118. Briley-Saebo KC, Mulder WJ, Mani V, et al. Magnetic resonance imaging of vulnerable atherosclerotic plaques: current imaging strategies and molecular imaging probes. *J Magn Reson Imaging* 2007;26(3):460–479.
119. Tan M, Wu X, Jeong EK, Chen Q, Parker DL, Lu ZR. An effective targeted nanoglobular manganese (II) chelate conjugate for magnetic resonance molecular imaging of tumor extracellular matrix. *Mol Pharm* 2010;7(4):936–943.
120. Xu C, Sun S. Superparamagnetic nanoparticles as targeted probes for diagnostic and therapeutic applications. *Dalton Trans* 2009(29):5583–5591.
121. Kelly KA, Bardeesy N, Anbazhagan R, et al. Targeted nanoparticles for imaging incipient pancreatic ductal adenocarcinoma. *PLoS Med* 2008;5(4):e85.
122. Yang L, Mao H, Wang YA, et al. Single chain epidermal growth factor receptor antibody conjugated nanoparticles for in vivo tumor targeting and imaging. *Small* 2009;5(2):235–243.
123. Gambhir SS, Czernin J, Schwimmer J, Silverman DH, Coleman RE, Phelps ME. A tabulated summary of the FDG PET literature. *J Nucl Med* 2001;42(5,Suppl):1S–93S.
124. Reske SN, Grillenberger KG, Glatting G, et al. Overexpression of glucose transporter 1 and increased FDG uptake in pancreatic carcinoma. *J Nucl Med* 1997;38(9):1344–1348.
125. Sperti C, Pasquali C, Decet G, Chierichetti F, Liessi G, Pedrazzoli S. F-18-fluorodeoxyglucose positron emission tomography in differentiating malignant from benign pancreatic cysts: a prospective study. *J Gastrointest Surg* 2005;9(1):22–28; discussion 28–29.
126. Bang S, Chung HW, Park SW, et al. The clinical usefulness of 18-fluorodeoxyglucose positron emission tomography in the differential diagnosis, staging, and response evaluation after concurrent chemoradiotherapy for pancreatic cancer. *J Clin Gastroenterol* 2006;40(10):923–929.
127. Wakabayashi H, Nishiyama Y, Otani T, et al. Role of 18F-fluorodeoxyglucose positron emission tomography imaging in surgery for pancreatic cancer. *World J Gastroenterol* 2008;14(1):64–69.
128. Lytras D, Connor S, Bosonnet L, et al. Positron emission tomography does not add to computed tomography for the diagnosis and staging of pancreatic cancer. *Dig Surg* 2005;22(1-2):55–61; discussion 62.
129. Nishiyama Y, Yamamoto Y, Monden T, et al. Evaluation of delayed additional FDG PET imaging in patients with pancreatic tumour. *Nucl Med Commun* 2005;26(10):895–901.
130. Singer E, Gschwantler M, Plattner D, et al. Differential diagnosis of benign and malignant pancreatic masses with 18F-fluorodeoxyglucose-positron emission tomography recorded with a dual-head coincidence gamma camera. *Eur J Gastroenterol Hepatol* 2007;19(6):471–478.
131. Borbath I, Van Beers BE, Lonneux M, et al. Preoperative assessment of pancreatic tumors using magnetic resonance imaging, endoscopic ultrasonography, positron emission tomography and laparoscopy. *Pancreatol* 2005;5(6):553–561.

132. Seo S, Doi R, Machimoto T, et al. Contribution of 18F-fluorodeoxyglucose positron emission tomography to the diagnosis of early pancreatic carcinoma. *J Hepatobiliary Pancreat Surg* 2008;15(6):634–639.
133. Ruf J, Lopez Hänninen E, Oettle H, et al. Detection of recurrent pancreatic cancer: comparison of FDG-PET with CT/MRI. *Pancreatology* 2005;5(2-3):266–272.
134. Sperti C, Pasquali C, Bissoli S, Chierichetti F, Liessi G, Pedrazzoli S. Tumor relapse after pancreatic cancer resection is detected earlier by 18-FDG PET than by CT. *J Gastrointest Surg* 2010;14(1):131–140.
135. Sendler A, Avril N, Helmberger H, et al. Preoperative evaluation of pancreatic masses with positron emission tomography using 18F-fluorodeoxyglucose: diagnostic limitations. *World J Surg* 2000;24(9):1121–1129.
136. Tang S, Huang G, Liu J, et al. Usefulness of 18F-FDG PET, combined FDG-PET/CT and EUS in diagnosing primary pancreatic carcinoma: a meta-analysis. *Eur J Radiol* 2011;78(1):142–150.
137. Delbeke D, Martin WH. PET and PET/CT for pancreatic malignancies. *Surg Oncol Clin N Am* 2010;19(2):235–254.
138. Yoshimoto M, Waki A, Yonekura Y, et al. Characterization of acetate metabolism in tumor cells in relation to cell proliferation: acetate metabolism in tumor cells. *Nucl Med Biol* 2001;28(2):117–122.
139. Zhao C, Chen Z, Ye X, et al. Imaging a pancreatic carcinoma xenograft model with 11C-acetate: a comparison study with 18F-FDG. *Nucl Med Commun* 2009;30(12):971–977.
140. Flores LG, Bertolini S, Yeh HH, et al. Detection of pancreatic carcinomas by imaging lactose-binding protein expression in peritumoral pancreas using [18F]fluoroethyl-deoxylactose PET/CT. *PLoS One* 2009;4(11):e7977.
141. Hausner SH, Abbey CK, Bold RJ, et al. Targeted in vivo imaging of integrin α v β 6 with an improved radiotracer and its relevance in a pancreatic tumor model. *Cancer Res* 2009;69(14):5843–5850.
142. Kimura RH, Teed R, Hackel BJ, et al. Pharmacokinetically stabilized cystine knot peptides that bind α v β 6 integrin with single-digit nanomolar affinities for detection of pancreatic cancer. *Clin Cancer Res* 2012;18(3):839–849.
143. Amirkhanov NV, Zhang K, Aruva MR, Thakur ML, Wickstrom E. Imaging human pancreatic cancer xenografts by targeting mutant KRAS2 mRNA with [(111)In]DOTA(n)-poly(diamidopropanoyl)(m)-KRAS2 PNA-D(Cys-Ser-Lys-Cys) nanoparticles. *Bioconjug Chem* 2010;21(4):731–740.
144. Chakrabarti A, Zhang K, Aruva MR, et al. Radiohybridization PET imaging of KRAS G12D mRNA expression in human pancreas cancer xenografts with [(64)Cu]DO3A-peptide nucleic acid-peptide nanoparticles. *Cancer Biol Ther* 2007;6(6):948–956.
145. Mosessian S, Duarte-Vogel SM, Stout DB, et al. INDs for PET molecular imaging probes—approach by an academic institution. *Mol Imaging Biol* 2014;16(4):441–448.