Published in final edited form as:

Cancer J. 2015 ; 21(3): 188–193. doi:10.1097/PPO.0000000000000109.

Challenges of Pancreatic Cancer

Julien Dimastromatteo^{1,†}, Jacob L. Houghton^{2,†}, Jason S. Lewis², and Kimberly A. Kelly¹

¹Biomedical Engineering Department, University of Virginia, Robert M. Berne Cardiovascular Research Center, Charlottesville, VA

²Department of Radiology and the Program in Molecular Pharmacology and Chemistry, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Abstract

The development of novel molecular cancer imaging agents has considerably advanced in recent years. Numerous cancer imaging agents have demonstrated remarkable potential for aiding the diagnosis, staging, and treatment planning at the preclinical stage which in turn has led to a number of agents being approved for human trials. Pancreatic ductal adenocarcinoma (PDAC) is currently the most deadly common carcinoma with an overall 5-year survival rate of about 6%. As detection technologies progress, the need for molecular imaging tools that will allow the diagnosis at an early stage will be crucial to improving patient outcomes. In this review, we will highlight agents that illuminate various cell populations that comprise the tumor: epithelial, endothelial, and stromal tumor cells.

Keywords

Pancreatic Cancer; Molecular Imaging; molecular imaging agents

Introduction

The development of novel molecular imaging agents has advanced at an exceptional rate in recent years. Numerous imaging agents have demonstrated remarkable potential for aiding the diagnosis, staging, and treatment planning at the preclinical stage which in turn has led to a number of agents being approved for human trials. The understanding of the biology of many cancers, including the role of the tumor microenvironment, has expanded rapidly in the past decade and this is beginning to lead to rapid advances in the development of molecular imaging agents for various cancers.

Pancreatic ductal adenocarcinoma (PDAC) is currently the most deadly common carcinoma with an overall 5-year survival rate of about 6%. For the 25% of patients who qualify for surgical resection, the only cure for the disease, the 5-year survival rate is still only 20%. [1–3] The dire prognosis for PDAC patients is largely due to the inadequacy of the tools and

Corresponding author: Kimberly Kelly, PhD, Biomedical Engineering Department, University of Virginia, Robert M. Berne Cardiovascular Research Center, 415 Lane Road Bldg MR5 Rm 1214, Charlottesville, VA 22908, 434-243-9352, kak3x@eservices.virginia.edu.

[†]indicates authors with an equal contribution to this manuscript

treatments available for combating the disease, and recent advances in chemotherapy for PDAC patients have only marginally increased survival. [4–9] The complications associated with the diagnosis, staging, and treatment of PDAC could potentially be alleviated by the intelligent design and implementation of novel molecular imaging techniques, which could in turn improve the outcomes for PDAC patients.

Currently, due to the low incidence of pancreatic cancer and the limitations of current technologies, it is not feasible or cost effective to screen the general population for cases of sporadic cancer. However, there are patient populations with a high heightened risk of developing PDAC that are currently being screened, and as our understanding of PDAC-related serum biomarkers increases, it will become easier to develop more efficient screens to identify at risk individuals within the general population. As these technologies progress, the need for complementary molecular imaging tools that will allow the diagnosis at an early stage will be crucial to improving patient outcomes. In the following sections, we will highlight agents that illuminate various cell populations that comprise the tumor: epithelial, endothelial, and stromal tumor cells.

Tumor Endothelial Cells

Ultrasound is an inexpensive, portable, noninvasive, and widely available imaging modality that could more easily be adapted to widespread screening of at-risk patients when compared to other functional imaging techniques like MRI and CT. With that in mind, researchers are currently working to develop techniques that take advantage of ultrasound technology and molecular targeting to generate molecular imaging tools for PDAC. Microbubbles are small, gas-filled microspheres with specific acoustic properties that make them a useful contrast agent for ultrasound imaging. Due to their size, microbubbles are restricted to the vascular compartment, so they can be used to identify areas of inflammation, atherosclerotic plaques, thrombi, and other cardiovascular pathologies. By coupling a targeting agent such as antibodies or peptides, cancer specific binding of the microbubbles to the tumor endothelial has been achieved with incredible results.

In one such study, Korpanty et al. used antibodies targeting protein antigens that are highly expressed in pancreatic tumors, such as vascular endothelial growth factor receptor 2 (VEGFR2), in orthotopic murine models of PDAC. VEGFR2 is a major contributor to tumor angiogenesis and is over-expressed on tumor endothelial cells of angiogenic vessels in pancreatic cancer [10–19] and in almost all cancers. In the study, Korpanty et al. demonstrated the effectiveness of using molecularly targeted microbubbles to monitor angiogenesis and changes in the vasculature in response to anticancer agents. [20] More recently, Deshpande et al. conjugated an anti-VEGFR2 antibody to microbubbles. [21] It was shown that contrast enhanced ultrasound could be used to monitor the expression levels of VEGFR2 in subcutaneous xenografts, suggesting the potential for stratifying patients as well as personalizing therapy.

Thymocyte differentiation antigen 1 (Thy1) was recently identified as a vascular marker in a proteomic screen comparing human PDAC to chronic pancreatitis and normal pancreas. [22] Foygel et al. demonstrated that Thy1 targeted microbubbles were able to accurately

differentiate PDAC in both xenograft and genetically engineered mouse models. [22] The results were significant when compared to pancreas imaging performed on normal animals or animals with chronic pancreatitis, a risk factor for pancreatic cancer (Fig. 1). Further, the microbubble enhanced ultrasound imaging was able to identify animals with PanIN III, an advanced precursor lesion that if identified and removed, could prevent pancreatic cancer.

Tumor Epithelial Cells

Claudin-4, a transmembrane protein that is a component of tight junctions in epithelial cells is up-regulated in PDAC and late-stage PanIN lesions. In addition to pancreatic cancer, claudin-4 is a potential target in chemotherapy-resistant ovarian cancer and other highly aggressive human epithelial tumors including breast and prostate cancer, making it attractive as a molecular imaging target. [23, 24] Moreover, targeting claudin-4 for therapy of PDAC was the subject of a recent review by Kojima et al. and a number of studies describing claudin-4 as a target for molecular imaging have recently been reported. [25] Neesse et al. assessed the ability of a naturally occurring peptide ligand for claudin-4 to detect tumors that overexpress claudin-4. [26] It was shown that carboxyl-terminal portion of Clostridium perfringens enterotoxin (C-CPE) binds with high affinity to Claudin-4, even when the amino-terminal portion (enterotoxin) of the protein is removed. A Cy5.5-coupled C-CPE was developed for imaging Claudin-4-positive lesions in murine models of PDAC with very promising results. Additionally, Foss et al. evaluated a ¹²⁵I-radiolabeled anti-Claudin-4 tracer in an experimental murine xenograft model. [27] An excellent tumor-to-muscle uptake ratio of over 6:1 was obtained 4 days post injection by ex vivo biodistribution analysis in a Panc1 xenograft model. Although the pharmacokinetic characteristics of the recently reported agents need improvement, anti-claudin-4 targeting vectors have shown immense promise as potential diagnostic imaging agents for PDAC.

Plectin-1 is a cytosolic scaffolding molecule and member of the cytolinkers family. Due to its mislocalization to the extracellular surface of PDAC and PanIN type III lesions, Plectin-1 has been identified as a relevant target for molecular imaging of pancreatic cancer. [28, 29] Expression of Plectin-1 in high-grade PanIN and PDAC is significantly amplified compared to normal pancreas, chronic pancreatitis, and low-grade PanIN with 87% sensitivity and 98% specificity. PDAC was identified with 100% sensitivity and specificity. [30] Plectin-1-Targeted Peptide (PTP), a promising molecular imaging agent for the early diagnosis of PDAC, was originally discovered by phage display screening and has been modified to include DOTA for ¹¹¹In-radiolabeling and evaluated in orthotopic L3.6pl and Panc1 mice. [31] In both models, imaging illuminated pancreatic tumors (Fig. 2) and metastases.

Stromal Cells

Studying the tumor biology has revealed that the tumor microenvironment or stroma has an important role in tumor biology and also furnishes a wealth of targets for molecular imaging. While the PanIN-3 lesions, PDAC precursor [32], have relatively low epithelial cell counts from a quantitative standpoint, the surrounding cancer-associated fibroblasts (CAFs) are much greater in quantity and represent a potential route for early detection of pancreatic

cancer. For every epithelial cell, there are an estimated 10–100x or more adjacent CAFs, distinctly abnormal.

Cathepsin E (Cath E) is an aspartic protease that is not expressed in healthy pancreatic tissue but is highly expressed in PDACs and PanIN lesions. Cruz-Monserrate et al. engineered a Cath E-activatable imaging probe labelled with Cy5.5. [33] The Cath E-activatable imaging probe consisted of an inert polyethylene glycol protected grafted D-polylysine copolymeric template and multiple copies of a Cy5.5 labelled Cath E selective peptide sequence. Due to the close proximity of the attached fluorochromes in the imaging probe, the probe remains optically quenched, until the Cath E enzyme acts on the peptide linkers and releases the fluorescent reporters. The authors demonstrated that the Cath E-activatable imaging probe selectively bound and was able to allow the visualization of PanIN and PDAC lesions. Alas, due to the limitations of optical imaging, this type of contrast agent wouldn't be applicable to non-invasive imaging but could be exploited in fluorescent endoscopic imaging or during surgery.

Secreted Protein Acidic and Rich in Cysteine (SPARC) is a protein that is present in aggressive cancers including prostate, breast, lung, ovarian, and pancreatic. A high level of SPARC expression correlates with a poor prognosis. Secreted by stromal cells like CAFs, SPARC plays an important role in cell-matrix adhesion. [34] [35] SPARC targeted peptides conjugated to fluorescent nanoparticles were able to delineate lung and bone metastases of prostate cancer [36]. Given the importance of SPARC to pancreatic cancer stroma, SPARC represents a target that may be useful for pancreatic cancer imaging.

Circulating Tumor Biomarkers

The diagnosis of PDAC is often based partially on the detection of elevated levels of circulating CA19.9 (sialyl Lewis^a) in sera. [37, 38] CA19.9 is a ligand for epithelial leukocyte adhesion molecules, and its overexpression is a key event in invasion and metastasis of many tumors, including PDAC tumors. [39] However, the use of assays to detect circulating CA19.9 antigen for the diagnosis of PDAC has significant shortcomings that limit its utility to the screening and identification of potentially at-risk patients. [7–9] While screening efforts to identify novel biomarkers is a promising course of action that led to the identification promising biomarkers like plectin-1 and claudin-4, it is also stands to reason that simply changing the manner in which a flawed biomarker is assayed could rescue its diagnostic utility. In the case of CA19.9 recent studies have endeavored to develop a tool that can discriminate the tissue site(s) of circulating biomarker production and clearly distinguish benign from malignant disease.

Towards that end, a number of anti-CA19.9 PET tracers have recently been reported, several of which are promising. The fully human mAb 5B1 which potently binds an extracellular epitope of CA19.9, was developed as a platform for immunoPET imaging of PDAC. [40] 5B1 was conjugated to desferrioxamine and radiolabeled with ⁸⁹Zr for PET imaging. Imaging studies showed excellent uptake and clearly delineated tumor tissue in numerous murine models of PDAC, outperforming FDG in a comparative study (Fig. 3). [41] One major concern that arose in the initial studies with 5B1 was the potential for circulating

CA19.9 to diminish the usefulness of 5B1. However, initial studies indicated that 5B1 was able to delineate the tumors in the context of shed antigen. In addition to 5B1, a number anti-CA19.9 antibody fragments have recently been reported. [42–44] Antibody fragments are expected to increase tumor penetration and reduce the lag time between injection and imaging, providing a benefit to patients in terms of time spent in the clinic and exposure to radiation. While initial results with many of the anti-CA19.9 tracers are promising, murine models lack any endogenous expression of CA19.9 and until more biologically relevant murine models are developed or clinical data in humans becomes available, the utility of these tracers will remain uncertain.

Conclusion

While molecular imaging has a history of success with many common cancers, including breast and prostate cancers, it has not, to date, been as effectively applied to pancreatic cancer. There are a number of reasons for this discrepancy but progress has accelerated in recent years, providing hope that molecular imaging technology will soon be as widely applicable to the treatment of pancreatic cancer. With pancreatic cancer projected to become the second-leading cause of cancer deaths in the United States by the year 2020, these advances cannot come fast enough. There are currently numerous clinical trials ongoing at cancer centers around the world aimed developing an arsenal of molecular imaging technologies that will improve patient outcomes in ways that conventional imaging technologies such as MRI and CT cannot. Molecular imaging has the benefit of being able to differentiating between tumor, healthy pancreas, or pancreatitis on a molecular level, while also providing anatomical information about tumors. Furthermore, molecular imaging may also be used to quantify levels of biomarkers in tumors, which has implications in the emerging field of personalized medicine.

References

1. Kalser MH, Barkin J, MacIntyre JM. Pancreatic cancer. Assessment of prognosis by clinical presentation. *Cancer*. 1985; 56:397–402. [PubMed: 4005804]
2. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. *CA Cancer J Clin*. 2010; 60:277–300. [PubMed: 20610543]
3. Cameron JL, Riall TS, Coleman J, Belcher KA. One thousand consecutive pancreaticoduodenectomies. *Ann Surg*. 2006; 244:10–15. [PubMed: 16794383]
4. Fröhlich A, Diederichs CG, Staib L, et al. Detection of liver metastases from pancreatic cancer using FDG PET. *J Nucl Med*. 1999; 40:250–255. [PubMed: 10025831]
5. Higashi T, Saga T, Nakamoto Y, et al. Diagnosis of pancreatic cancer using fluorine-18 fluorodeoxyglucose positron emission tomography (FDG PET) --usefulness and limitations in “clinical reality”. *Ann Nucl Med*. 2003; 17:261–279. [PubMed: 12932109]
6. Murakami K. FDG-PET for hepatobiliary and pancreatic cancer: Advances and current limitations. *World J Clin Oncol*. 2011; 2:229–236. [PubMed: 21611100]
7. Ballehaninna UK, Chamberlain RS. The clinical utility of serum CA 19-9 in the diagnosis, prognosis and management of pancreatic adenocarcinoma: An evidence based appraisal. *J Gastrointest Oncol*. 2012; 3:105–119. [PubMed: 22811878]
8. Goonetilleke KS, Siriwardena AK. Systematic review of carbohydrate antigen (CA 19-9) as a biochemical marker in the diagnosis of pancreatic cancer. *Eur J Surg Oncol*. 2007; 33:266–270. [PubMed: 17097848]

9. Kim H-R, Lee C-H, Kim YW, et al. Increased CA 19-9 level in patients without malignant disease. *Clin Chem Lab Med*. 2009; 47:750–754. [PubMed: 19402792]
10. Hicklin DJ, Ellis LM. Role of the vascular endothelial growth factor pathway in tumor growth and angiogenesis. *J Clin Oncol*. 2005; 23:1011–1027. [PubMed: 15585754]
11. Longo R, Cacciamani F, Naso G, Gasparini G. Pancreatic cancer: from molecular signature to target therapy. *Crit Rev Oncol Hematol*. 2008; 68:197–211. [PubMed: 18436450]
12. Korc M. Pathways for aberrant angiogenesis in pancreatic cancer. *Mol Cancer*. 2003; 2:8. [PubMed: 12556241]
13. Tonra JR, Deevi DS, Corcoran E, et al. Synergistic antitumor effects of combined epidermal growth factor receptor and vascular endothelial growth factor receptor-2 targeted therapy. *Clin Cancer Res*. 2006; 12:2197–2207. [PubMed: 16609035]
14. Spano J-P, Chodkiewicz C, Maurel J, et al. Efficacy of gemcitabine plus axitinib compared with gemcitabine alone in patients with advanced pancreatic cancer: an open-label randomised phase II study. *Lancet*. 2008; 371:2101–2108. [PubMed: 18514303]
15. Itakura J, Ishiwata T, Friess H, et al. Enhanced expression of vascular endothelial growth factor in human pancreatic cancer correlates with local disease progression. *Clin Cancer Res*. 1997; 3:1309–1316. [PubMed: 9815813]
16. Büchler P, Reber HA, Roth MM, et al. Target therapy using a small molecule inhibitor against angiogenic receptors in pancreatic cancer. *Neoplasia*. 2007; 9:119–127. [PubMed: 17356708]
17. Higgins KJ, Abdelrahim M, Liu S, et al. Regulation of vascular endothelial growth factor receptor-2 expression in pancreatic cancer cells by Sp proteins. *Biochem Biophys Res Commun*. 2006; 345:292–301. [PubMed: 16678129]
18. Luo J, Guo P, Matsuda K, et al. Pancreatic cancer cell-derived vascular endothelial growth factor is biologically active in vitro and enhances tumorigenicity in vivo. *Int J Cancer*. 2001; 92:361–369. [PubMed: 11291072]
19. Shi Q, Le X, Abbruzzese JL, et al. Constitutive Sp1 activity is essential for differential constitutive expression of vascular endothelial growth factor in human pancreatic adenocarcinoma. *Cancer Res*. 2001; 61:4143–4154. [PubMed: 11358838]
20. Korpany G, Carbon JG, Grayburn PA, et al. Monitoring response to anticancer therapy by targeting microbubbles to tumor vasculature. *Clin Cancer Res*. 2007; 13:323–330. [PubMed: 17200371]
21. Deshpande N, Ren Y, Foygel K, et al. Tumor angiogenic marker expression levels during tumor growth: longitudinal assessment with molecularly targeted microbubbles and US imaging. *Radiology*. 2011; 258:804–811. [PubMed: 21339349]
22. 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; 145:885–894. e3. [PubMed: 23791701]
23. Cocco E, Casagrande F, Bellone S, et al. Clostridium perfringens enterotoxin carboxy-terminal fragment is a novel tumor-homing peptide for human ovarian cancer. *BMC Cancer*. 2010; 10:349. [PubMed: 20598131]
24. Boylan KLM, Misemer B, De Rycke MS, et al. Claudin 4 is differentially expressed between ovarian cancer subtypes and plays a role in spheroid formation. *Int J Mol Sci*. 2011; 12:1334–1358. [PubMed: 21541062]
25. Kojima T, Kyuno D, Sawada N. Targeting claudin-4 in human pancreatic cancer. *Expert Opin Ther Targets*. 2012; 16:881–887. [PubMed: 22800288]
26. Neesse A, Hahnenkamp A, Griesmann H, et al. Claudin-4-targeted optical imaging detects pancreatic cancer and its precursor lesions. *Gut*. 2013; 62:1034–1043. [PubMed: 22677720]
27. Foss CA, Fox JJ, Feldmann G, et al. Radiolabeled anti-claudin 4 and anti-prostate stem cell antigen: initial imaging in experimental models of pancreatic cancer. *Mol Imaging*. 2007; 6:131–139. [PubMed: 17445507]
28. Kelly KA, Bardeesy N, Anbazhagan R, et al. Targeted nanoparticles for imaging incipient pancreatic ductal adenocarcinoma. 2008; 5:e85.

29. Shin SJ, Smith JA, Reznicek GA, et al. Unexpected gain of function for the scaffolding protein plectin due to mislocalization in pancreatic cancer. *Proceedings of the National Academy of Sciences*. 2013; 110:19414–19419.
30. Coté GA, Smith J, Sherman S, Kelly K. Technologies for imaging the normal and diseased pancreas. *Gastroenterology*. 2013; 144:1262–71. e1. [PubMed: 23622136]
31. Bausch D, Thomas S, Mino-Kenudson M, et al. Plectin-1 as a novel biomarker for pancreatic cancer. *Clin Cancer Res*. 2011; 17:302–309. [PubMed: 21098698]
32. Hruban RH, Maitra A, Goggins M. Update on pancreatic intraepithelial neoplasia. *Int J Clin Exp Pathol*. 2008; 1:306–316. [PubMed: 18787611]
33. Cruz-Monserrate Z, Abd-Elgalil WR, Grote T, et al. Detection of pancreatic cancer tumours and precursor lesions by cathepsin E activity in mouse models. *Gut*. 2012; 61:1315–1322. [PubMed: 22068166]
34. Lane TF, Sage EH. The biology of SPARC, a protein that modulates cell-matrix interactions. *FASEB J*. 1994; 8:163–173. [PubMed: 8119487]
35. Clark CJ, Sage EH. A prototypic matricellular protein in the tumor microenvironment--where there's SPARC, there's fire. *Journal of Cellular Biochemistry*. 2008; 104:721–732. [PubMed: 18253934]
36. Thomas S, Waterman P, Chen S, et al. Development of Secreted Protein and Acidic and Rich in Cysteine (SPARC) Targeted Nanoparticles for the Prognostic Molecular Imaging of Metastatic Prostate Cancer. *J Nanomed Nanotechnol*. 2011
37. Humphris JL, Chang DK, Johns AL, et al. The prognostic and predictive value of serum CA19.9 in pancreatic cancer. *Ann Oncol*. 2012; 23:1713–1722. [PubMed: 22241899]
38. Sugiura T, Uesaka K, Kanemoto H, et al. Serum CA19-9 is a significant predictor among preoperative parameters for early recurrence after resection of pancreatic adenocarcinoma. *J Gastrointest Surg*. 2012; 16:977–985. [PubMed: 22411488]
39. Kannagi R, Izawa M, Koike T, et al. Carbohydrate-mediated cell adhesion in cancer metastasis and angiogenesis. *Cancer Sci*. 2004; 95:377–384. [PubMed: 15132763]
40. Sawada R, Sun S-M, Wu X, et al. Human monoclonal antibodies to sialyl-Lewis (CA19.9) with potent CDC, ADCC, and antitumor activity. *Clin Cancer Res*. 2011; 17:1024–1032. [PubMed: 21343375]
41. Viola-Villegas NT, Rice SL, Carlin S, et al. Applying PET to broaden the diagnostic utility of the clinically validated CA19.9 serum biomarker for oncology. *J Nucl Med*. 2013; 54:1876–1882. [PubMed: 24029655]
42. Rochefort MM, Girgis MD, Knowles SM, et al. A mutated anti-CA19-9 scFv-Fc for positron emission tomography of human pancreatic cancer xenografts. *Mol Imaging Biol*. 2014; 16:721–729. [PubMed: 24691872]
43. Girgis MD, Kenanova V, Olafsen T, et al. Anti-CA19-9 diabody as a PET imaging probe for pancreas cancer. *J Surg Res*. 2011; 170:169–178. [PubMed: 21601881]
44. Girgis MD, Federman N, Rochefort MM, et al. An engineered anti-CA19-9 cys-diabody for positron emission tomography imaging of pancreatic cancer and targeting of polymerized liposomal nanoparticles. *J Surg Res*. 2013; 185:45–55. [PubMed: 23827791]

Fig. 1.

In vivo ultrasound molecular imaging of a transgenic pancreatic tumor, chronic pancreatitis, and normal pancreas tissue and corresponding ex vivo immunofluorescence analysis. (A) Transverse ultra- sound images obtained in contrast mode after intravenous injection of murine Thy1-targeted MB show strong imaging signal in pancreatic tumor and a low signal after MBControl. Note low imaging signal after MBThy1 or MBControl in chronic pancreatitis and normal pancreas tissue (scale bar 1/4 5 mm; color coded scale is shown for ultrasound molecular imaging signal in arbitrary units). (B) Tiled confocal micrographs of murine Thy1 expression in a transgenic pancreatic tumor (top), chronic pancreatitis (middle), and WT pancreas (bottom) with murine Thy1 in red and CD31 in green show expression of murine Thy1 on the tumor vasculature but no expression on the vasculature in chronic pancreatitis and normal WT tumor.

Fig. 2.

In vivo imaging of Plec1 in orthotopic PDAC. A, in vitro validation of tPTP. L3.6pl cells were plated on a 96-well plate and incubated with ^{111}In -tPTP and increasing log concentrations of unlabeled tPTP or negative control tetramer. B, mice bearing tumors from orthotopically implanted L3.6pl, AK134 cells, and mice without tumors (null) were injected with ^{111}In -tPTP and imaged via SPECT/CT 4 hours postinjection. Note the accumulation of tPTP in PDAC, allowing the in vivo imaging of tumor in the pancreas and in peritoneal metastases. Coronal (left) and axial (right) SPECT/CT slices through the tumor are presented. T, tumor; K, kidney; M, peritoneal metastasis. C, after SPECT/CT imaging, animals were sacrificed, organs harvested, and gamma counts assessed. Null data are from both nu/nu and FVB/NJ animals that were injected in the pancreas with saline. D, histology. Animals that had orthotopically implanted tumors or null animals were sacrificed and pancreas and regions of visible peritoneal metastases were removed, embedded, sectioned, and stained with H&E (20 image). PT, primary tumor; PM, peritoneal metastasis.

Fig. 3.

Correlative imaging of orthotopically transplanted BxPC3-luc pancreatic tumor. Bioluminescent optical imaging (BLI) demonstrated the presence tumors in the area of surgical transplantation (A). Magnetic resonance imaging validated the observed tumor presence from BLI (B). Regions-of-interest (C, left) obtained from FDG (n=10) and ^{89}Zr -5B1 (n=5) PET images demonstrate a mean tumor uptake of 4.8 ± 1.3 %ID/g for FDG while tumor accretion demonstrated by ^{89}Zr -5B1 at 48 h p.i. was 30.7 ± 6.6 %ID/g ($P < 0.001$). Tumor-to-muscle ratios (T/M, C, right) determined for ^{89}Zr -5B1 were 6.2 ± 2.3

(2 h), 11.0 ± 1.9 (24 h), 20.9 ± 3.9 (48 h), 21.2 ± 4.7 (96 h) and 22.7 ± 5.9 (120 h) while FDG provided a 3.5 ± 1.1 tumor-to-muscle contrast ratio ($P < 0.001$). The co-registration of FDG-PET and CT (left) and planar sections of FDG-PET only (right) displayed minimal tumor detection of the tracer with a high uptake in highly metabolic tissues (i.e. heart) (D). Acquired ^{89}Zr -5B1 PET image of the same mouse co-registered with CT exhibited exceptional tumor detection of the BxPC3-luc tumor xenografts (E). This research was originally published in *JNM*. Reference [41] © by the Society of Nuclear Medicine and Molecular Imaging, Inc.