Published in final edited form as:

Clin Nucl Med. 2016 March ; 41(3): 177–181. doi:10.1097/RLU.0000000000001098.

Metabolic Activity by (18)F-FDG-PET/CT is Prognostic for Stage I and II Pancreatic Cancer

Jose M. Pimiento, MD¹, Ashley H. Davis-Yadley, MD^{1,2}, Richard D. Kim, MD¹, Dung-Tsa Chen, PhD¹, Edward A. Eikman, MD¹, Claudia G. Berman, MD¹, and Mokenge P. Malafa, MD¹

¹Surgical Oncology, H Lee Moffitt Cancer Center and Research Institute, Tampa, FL, United States

²Internal Medicine, University of South Florida Morsani College of Medicine, Tampa, FL, United States

Abstract

Purpose—Metabolic activity, as defined by 18F-fluorodeoxyglucose (FDG) uptake on positron emission tomography (PET), is a prognostic marker for multiple malignancies; however, no study has examined the prognostic value of imaging with FDG PET in stage I and II pancreatic cancer. We examined the value of PET FDG uptake in early-stage pancreatic cancer patients.

Methods—We identified patients with early-stage pancreatic cancer (I–II) who had FDG PET scan performed as part of their preoperative evaluation. Patients were divided by the median primary tumor standard uptake value (SUVmax) into either high or low FDG uptake. Our primary endpoints were overall survival (OS) and recurrence-free survival (RFS). Kaplan-Meier estimate was used for survival analysis. Pathologic data were compared using Fisher's exact and chi-square tests.

Results—105 patients were identified: 51 patients with low-FDG uptake and 54 patients with high-FDG uptake. Eighty-five (81%) patients had PET avid tumors, whereas 20 (19%) patients did not. High-FDG uptake correlated with pathologic stage ($P=0.012$). Patients with low-FDG uptake had significantly better median OS than patients with high-FDG uptake (28 vs. 16 months; $P=0.036$). Patients with low-FDG uptake had significantly longer median RFS than patients with high FDG uptake (14 vs. 12 months; $P=0.049$).

Conclusions—Low FDG uptake in PET scans in patients with stage I and II pancreatic cancer correlates with improved OS and RFS. This supports the concept that glucose metabolic pathways are important in pancreatic cancer biology and that PET scan activity can be used as a prognostic biomarker after pancreatectomy.

Corresponding author: Mokenge P. Malafa, MD, Gastrointestinal Tumor Program, H. Lee Moffitt Cancer Center and Research Institute, 12902 Magnolia Drive, Tampa, Florida 33692 (Mokenge.malafa@moffitt.org; Tel: 8137451432).

DISCLOSURES

Potential competing interests: None

Conflict of Interest: All authors declare no conflict of interest.

Keywords

PET; SUV; pancreatic cancer; prognosis

INTRODUCTION

Metabolic activity, as defined by the uptake of 18F-fluorodeoxyglucose (FDG) on positron emission tomography (PET), takes advantage of the physiologic preferential use of anaerobic glycolysis over oxidative phosphorylation used by malignant cells for their energetic needs.^{1,2} This phenomenon, known as the Warburg effect, has recently been revived with the clinical use of PET and verified with the tracer FDG.³ A higher rate of ATP generation is observed if cellular respiration occurs through glycolysis, enabling cancer cells to gain a competitive advantage for shared energy resources such as glucose.³ Given that cancer cells employ an increased need for glucose and that FDG, an analogue of glucose, can be used with PET imaging, the increased uptake of FDG on PET can potentially be associated with a poor prognosis in patients with early-stage pancreatic cancer. Imaging of FDG with PET has also been used successfully as a diagnostic and prognostic marker for multiple malignancies and is used routinely in the work-up and follow-up of a number of different diseases, including advanced malignant melanoma, esophageal cancer, lung cancer, and breast cancer.^{4–10} Anti-cancer therapies that target glucose metabolism in cancer cells have also been recently investigated.³

Current guidelines for the staging and follow-up of pancreatic cancer do not include PET as a method for diagnosis or staging for this disease.¹¹ However, our group reported a 10% rate of up-staging in patients diagnosed with resectable pancreatic cancer by including a PET scan in their staging work-up, leading to changes in the testing of our pancreatic cancer patients.¹² Others have assigned importance in the evaluation of hypermetabolic lesions in patients with cystic lesions of the pancreas,^{13–15} and reports have been published regarding the value of FDG uptake as a marker of response to definitive chemoradiation in patients with locally advanced pancreatic carcinoma.¹⁶ However, no study has examined the prognostic value of PET in stage I and II pancreatic cancer. Therefore, in light of these previous reports, our goal was to evaluate the prognostic value of hypermetabolic activity as indicated by FDG uptake in patients with a diagnosis of early pancreatic cancer, to help inform on the possible value of PET in this lethal disease.

METHODS

Patients

In 2005, following Institutional Review Board (IRB) approval, the Gastrointestinal Oncology Department at Moffitt Cancer Center established a database of pancreatic cases by performing a retrospective chart review of patients operated on at Moffitt starting as far back as 1987, which has continued to this date. Data collected for this database include patient demographics, pre-neoadjuvant treatment clinical assessment, post-neoadjuvant treatment clinical assessment, surgical procedure details, pathological tumor stage and histopathologic features, peri-operative events, and complications. The diagnosis of pancreatic cancer was

confirmed by pathological analysis of a surgical specimen in patients with resectable disease. Chart reviews were performed solely by experienced clinicians and recorded on standardized abstraction forms. Data were entered into a Microsoft Access database by a data analyst, and ambiguities in any data points were discussed, researched, reviewed, and corrected. We queried this database for patients who had undergone operations at Moffitt between February 2004 and December 2010, focusing on those patients who had PET scans or were available for review as part of the pre-operative staging work-up. This study focused on patients with stage I and II pancreatic ductal adenocarcinoma, and treatment of patients was according to NCCN guidelines.¹¹ In brief, all patients had curative surgical resection and adjuvant chemotherapy and chemoradiation therapy. All procedures were performed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2005.

Surgical procedures

Surgical procedures included standard pancreaticoduodenectomy for tumors of the head and uncinate process and distal pancreatectomy and splenectomy for tumors of the neck, body, and tail. For vascular reconstruction, when needed, we used the internal saphenous vein, harvested from the groin of the patients. The patients were seen in clinic approximately 1 month after surgery if they had any surgical procedure and then every 3–4 months thereafter as described before.¹⁶

¹⁸F-fluorodeoxyglucose positron emission tomography protocol and analysis

For FDG PET scans in patients with pancreatic cancer who are scheduled for resective surgery at our institution, non-diabetic patients are asked to fast for at least 4 hours and diabetic patients are asked to fast for at least 6 hours before scanning. Blood glucose concentrations are measured to ensure that glucose levels do not exceed 200 mg/dL before intravenous injection of FDG. There is then about a 90-minute interval between administration of 10 mCi FDG intravenously and the acquisition of the emission images to ensure adequate biodistribution of FDG. The average scan time is 3 minutes per bed, with there being 7 or 8 beds total. The normal slice thickness is 3.75 mm. We perform FDG studies with a dedicated PET/CT scanner, the GE-Discovery DVCT-PET/CT (GE Medical Systems, Milwaukee, WI), which has a 70-cm aperture, 15-cm axial field of view, a 64-slice CT scanner, and a LYSO crystal-based PET scanner. This scanner includes a BGO block detector system and has a crystal size of 4.7 mm transaxially, 6.3 mm axially, and 30 mm radially. The axial sampling interval is 3.27 mm. PET images are reviewed by a board-certified nuclear medicine physician, and tumors are defined as having positive FDG uptake if the radioactivity of the tumor is higher than that of the surrounding tissue in visual analyses. Images are then assessed semi-quantitatively by measuring and calculating the median primary tumor standard uptake value (SUV_{max}) normalized to lean body mass.

Statistical analysis

In our analyses, we found that the median SUV_{max} by the pancreatic tumors was 5.1 (0–27.1). We decided to base our analyses around this median SUV_{max} and thus divided patients into those with high-FDG uptake (>median SUV_{max}) and those with low-FDG uptake. For analysis, we used chi-squared or Fisher's exact tests as appropriate for

categorical data, and mean differences were examined for continuous data using ANOVA. All statistical tests performed were two-sided and declared at the 5% significance level. The primary outcomes were overall survival and recurrence-free survival. Overall survival was calculated from the date of surgery until the date of death or last contact. Recurrence-free survival was calculated from the date of surgery until the last date at which the patient was known to be free of disease. Overall survival and recurrence-free survival curves were created by the Kaplan–Meier method. Statistical analyses were performed with STATA 10 (Stata Statistical Software, Release 10.0; Strata Corp., College Station, TX).

RESULTS

Clinicopathological characteristics of patients

We identified 164 patients who underwent pancreatic resection for histologically proven pancreatic adenocarcinoma stage I and II. Of these patients, 105 had PET scans performed as part of their preoperative staging work-up and were available for review (mean age at diagnosis of 67 (24 to 89) years, with 60 male patients (57%)). Eighty-five (81%) patients displayed PET avid tumors, whereas lack of FDG uptake was seen in 20 patients (19%) (Figure 1). The median PET SUVmax was 5.1 (0–27.1). Based on this value, we divided patients into two groups: low-FDG and high-FDG uptake, with 51 patients having low-FDG uptake and 54 patients having high-FDG uptake. When we compared the two groups, we found no statistically significant differences in gender, tumor grade, or nodal stage, although significance was almost reached for T stage (Table 1). However, we found that low uptake was correlated with lower overall pathologic stage than high uptake. At our institution, we only use neoadjuvant therapy for patients with borderline resectable tumors as defined by the AHPBA and the NCCN.¹¹ When assessing our data, we found that administration of neoadjuvant and adjuvant chemotherapy was not different for the low-FDG versus high-FDG uptake groups.

FDG PET uptake correlates with overall survival and recurrence-free survival

We found that overall survival was correlated with preoperative PET FDG uptake, which was 28 months (95% confidence interval (CI): 22–32 months) in patients with low FDG vs. 16 months (95% CI: 10–21 months) ($P=0.036$) in high-FDG uptake patients (Figure 2). Recurrence-free survival was 14 months (95% CI: 10.9–17 months) vs. 12 months (95% CI: 10–21 months) ($P=0.049$) (Figure 3) in low- and high-FDG patients, respectively. Median follow-up of patients was 12.3 (0–56) months. Moreover, on multiple regression analysis, we found that high-FDG uptake (hazard ratio (HR) 2.1; 95% CI: 1.59–5; $P=0.02$) and poor histologic differentiation (HR 2.1; 95% CI: 1.1–4.1; $P=0.014$) were independent factors associated with decreased survival in this cohort of patients. Although stage IIB was associated with decreased survival, it did not reach statistical significance in this analysis (Table 2).

DISCUSSION

Pancreatic cancer is the 4th leading cause of cancer death,¹⁸ with a dismal 5-year survival after surgical resection for patients who have early-stage (stage I–II) disease. Although

pancreatectomy is plagued by high morbidity, it is the only curative option for this disease.^{18–20} Efforts are underway to identify biomarkers that will predict patients with favorable tumor biology who would benefit the most from surgical treatment as well as to identify patients in which pancreatectomy would be associated with a suboptimal survival benefit.^{21,22} In this regard, markers such as elevated blood levels of Ca19-9 predict low resectability rate and poor survival rates.^{22,23} PET SUV in pancreatic adenocarcinoma patients may also prove to be useful as a biomarker for evaluation of overall and recurrence-free survival, providing information to help guide surgical and medical management of these patients.

In other malignant diseases, FDG uptake has been used as a biomarker,²⁴ including in a study that showed increased metabolic uptake in pre-treatment assessments correlated with worse response to chemoradiation in locally advanced hepatocellular carcinoma.²⁵ In 2009, Lee et al proposed that a high SUVmax in patients with hepatocellular carcinoma who underwent liver transplantation was the most significant predictor of recurrence, with similar findings seen by others.^{26,27} The degree of “hypermetabolism” was also shown to correlate with outcomes and response to treatment in patients with aero-digestive tract malignancies.^{7,10} Recent reports have highlighted the value of PET scanning in the diagnosis of indeterminate pancreatic masses, showing that it might add to the information obtained by contrast imaging.^{14,15,28–31} In this context, we found that patients who had low-FDG uptake in PET scans for stage I and II pancreatic cancer showed improved overall survival and recurrence-free survival when compared with patients who had high-FDG uptake. Moreover, although significance was not reached ($P=0.3$) when we examined the 19% of patients who had no FDG uptake, there was a trend toward improved outcomes in PET-negative patients as median OS was not reached versus that shown in patients who had any FDG uptake (median OS of 21 months (CI 95%: 13–28 months). This observation supports the concept that glucose metabolic pathways are important in pancreatic cancer biology and that, preoperatively, PET scan activity can be used as a prognostic biomarker after pancreatectomy in patients with pancreatic cancer. It also brings to the forefront the fact that not all pancreatic adenocarcinomas are metabolically active and forewarns the use of the lack of FDG uptake as a marker of benign disease. The high percentage of PET-negative tumors in our study, which appears to be higher than other groups, further makes it unlikely that negative PET activity alone is enough to rule out cancer.

Our study has several limitations: first that it is a database review and also that the PET scans were performed over a large period of time (2004–2010). We aimed to overcome these limitations by performing a review of each PET scan on the same software by the same reviewer. Our main strength is the fact that most of our resected patients over this period of time, 105 of 164, underwent PET scanning as part of our institutions staging work-up, allowing us to define patterns of glucose uptake in pancreatic cancer and also to evaluate small differences in the low- and high-uptake groups.

In conclusion, we demonstrated that low FDG uptake in PET scans for stage I and II pancreatic cancer correlates with improved overall survival and disease-free survival. This supports the notion that glucose metabolic pathways have a role in pancreatic cancer biology and that PET scan activity may be used as a prognostic tool after pancreatectomy in patients

with pancreatic cancer. Our study further suggests that patients with high FDG uptake may need to be considered as high-risk individuals when making a decision to perform pancreatectomies in patients with early pancreatic cancer. This alternative prognostic tool may help to determine those patients who will benefit the most from surgical resection.

ACKNOWLEDGMENTS

We thank Rasa Hamilton (Moffitt Cancer Center) for editorial assistance.

Financial support: The study was supported in part by National Cancer Institute/USPHS Grant IRO1 CA-129227-01A1. This was an independent study without the role of any study sponsors.

REFERENCES

1. Warburg O. On the origin of cancer cells. *Science*. 1956; 123:309–314. [PubMed: 13298683]
2. Higashi K, Clavo AC, Wahl RL. Does FDG uptake measure proliferative activity of human cancer cells? In vitro comparison with DNA flow cytometry and tritiated thymidine uptake. *J Nucl Med*. 1993; 34:414–419. [PubMed: 8441032]
3. Upadhyay M, Samal J, Kandpal M, Singh OV, Vivekanandan P. The Warburg effect: Insights from the past decade. *Pharmacol Therap*. 2013; 137:318–330. [PubMed: 23159371]
4. MacManus MP, Seymour JF, Hicks RJ. Overview of early response assessment in lymphoma with FDG-PET. *Cancer Imaging*. 2007; 7:10–18. [PubMed: 17766210]
5. Dickson MA, Okuno SH, Keohan ML, et al. Phase II study of the HSP90-inhibitor BIIB021 in gastrointestinal stromal tumors. *Ann Oncol*. 2013; 24:252–257. [PubMed: 22898035]
6. Baudy AR, Dogan T, Flores-Mercado JE, Hoeflich KP, Su F, van Bruggen N, Williams SP. FDG-PET is a good biomarker of both early response and acquired resistance in BRAFV600 mutant melanomas treated with vemurafenib and the MEK inhibitor GDC-0973. *EJNMMI Res*. 2012; 2:22. [PubMed: 22651703]
7. Suzuki H, Kato K, Fujimoto Y, et al. (18)F-FDG-PET/CT predicts survival in hypopharyngeal squamous cell carcinoma. *Ann Nucl Med*. 2013; 27:297–302. [PubMed: 23337965]
8. zum Buschenfelde CM, Herrmann K, Schuster T, et al. (18)F-FDG PET-guided salvage neoadjuvant radiochemotherapy of adenocarcinoma of the esophagogastric junction: the MUNICON II trial. *J Nucl Med*. 2011; 52:1189–1196. [PubMed: 21764790]
9. Lam WW, Loke KS, Loi HY, Padhy AK. Pancreatic metastasis detected by F-18 FDG PET/CT in a patient with breast cancer. *Clin Nucl Med*. 2011; 36:479–480. [PubMed: 21552032]
10. Fischer B, Lassen U, Mortensen J, et al. Preoperative staging of lung cancer with combined PET-CT. *N Engl J Med*. 2009; 361:32–39. [PubMed: 19571281]
11. Tempero MA, Arnoletti JP, Behrman SW, et al. Pancreatic Adenocarcinoma, version 2.2012: featured updates to the NCCN Guidelines. *J Natl Compr Cancer Netw*. 2012; 10:703–713.
12. Farma JM, Santillan AA, Melis M, et al. PET/CT fusion scan enhances CT staging in patients with pancreatic neoplasms. *Ann Surg Oncol*. 2008; 15:2465–2471. [PubMed: 18551347]
13. Nair RM, Barthel JS, Centeno BA, Choi J, Klapman JP, Malafa MP. Interdisciplinary management of an intraductal papillary mucinous neoplasm of the pancreas. *Cancer Control*. 2008; 15:322–333. [PubMed: 18813200]
14. Baiocchi GL, Bertagna F, Gheza F, et al. Searching for indicators of malignancy in pancreatic intraductal papillary mucinous neoplasms: the value of 18FDG-PET confirmed. *Ann Surg Oncol*. 2012; 19:3574–3580. [PubMed: 22752369]
15. Konstantinou F, Syrigos KN, Saif MW. Intraductal papillary mucinous neoplasms of the pancreas (IPMNs): epidemiology, diagnosis and future aspects. *JOP*. 2013; 14:141–144. [PubMed: 23474557]
16. Topkan E, Parlak C, Kotek A, Yapar AF, Pehlivan B. Predictive value of metabolic 18FDG-PET response on outcomes in patients with locally advanced pancreatic carcinoma treated with definitive concurrent chemoradiotherapy. *BMC Gastroenterol*. 2011; 11:123. [PubMed: 22074002]

17. Patel M, Hoffe S, Malafa M, et al. Neoadjuvant GTX chemotherapy and IMRT-based chemoradiation for borderline resectable pancreatic cancer. *J Surg Oncol.* 2011; 104:155–161. [PubMed: 21520097]
18. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. *CA Cancer J Clin.* 2013; 63:11–30. [PubMed: 23335087]
19. Turrini O, Paye F, Bachellier P, et al. Pancreatectomy for adenocarcinoma in elderly patients: postoperative outcomes and long term results: a study of the French Surgical Association. *Eur J Surg Oncol.* 2013; 39:171–178. [PubMed: 22999411]
20. Witkowski ER, Smith JK, Tseng JF. Outcomes following resection of pancreatic cancer. *J Surg Oncol.* 2013; 107:97–103. [PubMed: 22991309]
21. Einama T, Kamachi H, Nishihara H, et al. Co-expression of mesothelin and CA125 correlates with unfavorable patient outcome in pancreatic ductal adenocarcinoma. *Pancreas.* 2011; 40:1276–1282. [PubMed: 21775916]
22. Ferrone CR, Finkelstein DM, Thayer SP, Muzikansky A, Fernandez-delCastillo C, Warshaw AL. Perioperative CA19-9 levels can predict stage and survival in patients with resectable pancreatic adenocarcinoma. *J Clin Oncol.* 2006; 24:2897–2902. [PubMed: 16782929]
23. Hartwig W, Strobel O, Hinz U, et al. CA19-9 in potentially resectable pancreatic cancer: perspective to adjust surgical and perioperative therapy. *Ann Surg Oncol.* 2012; 18:18.
24. Shiomi S, Nishiguchi S, Ishizu H, et al. Usefulness of positron emission tomography with fluorine-18-fluorodeoxyglucose for predicting outcome in patients with hepatocellular carcinoma. *Am J Gastroenterol.* 2001; 96:1877–1880. [PubMed: 11419843]
25. Kim BK, Kang WJ, Kim JK, et al. 18F-fluorodeoxyglucose uptake on positron emission tomography as a prognostic predictor in locally advanced hepatocellular carcinoma. *Cancer.* 2011; 117:4779–4787. [PubMed: 21469082]
26. Lee JW, Paeng JC, Kang KW, et al. Prediction of tumor recurrence by 18F-FDG PET in liver transplantation for hepatocellular carcinoma. *J Nucl Med.* 2009; 50:682–687. [PubMed: 19372474]
27. Kornberg A, Kupper B, Thrum K, et al. Increased 18F-FDG uptake of hepatocellular carcinoma on positron emission tomography independently predicts tumor recurrence in liver transplant patients. *Transplant Proc.* 2009; 41:2561–2563. [PubMed: 19715974]
28. Javery O, Shyn P, Morte K. FDG PET or PET/CT in patients with pancreatic cancer: when does it add to diagnostic CT or MRI? *Clin Imaging.* 2013; 37:295–301. [PubMed: 23465982]
29. Dibble EH, Karantanis D, Mercier G, Peller PJ, Kachnic LA, Subramaniam RM. PET/CT of cancer patients: part 1, pancreatic neoplasms. *Am J Roentgenol.* 2012; 199:952–967. [PubMed: 23096166]
30. Serrano OK, Chaudhry MA, Leach SD. The role of PET scanning in pancreatic cancer. *Adv Surg.* 2010; 44:313–325. [PubMed: 20919529]
31. Kauhanen SP, Komar G, Seppanen 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; 250:957–963. [PubMed: 19687736]

Figure 1. FDG Uptake

Low vs. high FDG uptake is displayed in the following CT and PET scans.

Figure 2. Overall survival

Patients with low-FDG uptake had significantly better median overall survival than patients with high-FDG uptake.

Figure 3. Recurrence-free survival

Patients with low-FDG uptake had significantly longer median recurrence-free survival than patients with high-FDG uptake.

Table 1

Differences between low and high SUV max groups in patients

Characteristics	Total	SUV <5	SUV >5	P
T stage				0.075
T1	15 (14%)	11 (21%)	4 (7%)	
T2	14 (13%)	7 (14%)	7 (13%)	
T3	76 (73%)	33 (64.7%)	43 (80%)	
N stage				0.24
N0	51 (49%)	28 (54%)	23 (43%)	
N1	54 (51%)	23 (46%)	31 (57%)	
Stage				0.03
I	21 (20%)	15 (29%)	6 (11%)	
II	84 (80%)	36 (71%)	48 (89%)	
Sex				0.32
Female	45 (43%)	19 (37%)	26 (48%)	
Male	60 (57%)	32 (63%)	28 (52%)	
Grade (n=96)				0.692
Well differentiated	14 (15%)	7 (15%)	7 (14%)	
Moderately differentiated	53 (55%)	27 (59%)	26 (52%)	
Poorly differentiated	29 (30%)	12 (26%)	17 (34%)	
Chemotherapy				0.4
Neoadjuvant	31 (30%)	13 (25%)	18(33%)	
Adjuvant only	66 (63%)	34 (66%)	32 (59%)	

Table 2

Multivariate analysis for factors associated with overall survival

Characteristics	HR (95% CI)	<i>P</i>
Gender		0.1
Female	0.51 (0.25–1.1)	
Grade		0.014
Poorly differentiated	2.1 (1.1–4.1)	
AJCC 6 th		0.06
Stage IIB	3.1 (0.95–11.18)	
Neoadjuvant Therapy		0.7
No	0.84 (0.3–1.9)	
SUV max		0.02
SUV>5	2.45 (1.59–5.04)	