ORIGINAL ARTICLE

An Assessment of Positron Emission Tomography in the Evaluation of Patients with Pancreatic Ductal Adenocarcinoma

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ABSTRACT

Background Pancreatic ductal adenocarcinoma is an aggressive disease in which accurate staging is critical. Positron emission tomography has shown promise as a method of detecting metastatic disease in many cancers, but data supporting its use in pancreatic ductal adenocarcinoma is controversial. This study evaluated the impact of positron emission tomography on treatment in patients with pancreatic ductal adenocarcinoma. **Methods** A retrospective chart review identified patients with pancreatic ductal adenocarcinoma diagnosed between 2004-2012 who received positron emission tomography imaging as part of their disease assessment. The impact of positron emission tomography on therapy decisions was determined. **Results** Of the 62 patients evaluated, 7 (11.3%) had imaging prior to adjuvant therapy, 34 (54.8%) prior to neoadjuvant therapy, and 21 (33.9%) as part of initial staging. The median overall survival was 10.3 months (range: 1–31.6) and 14 patients (22.6%) underwent pancreatectomy. Positron emission tomography changed the treatment pathway in 6 patients (9.7%) including: 2/34 being staged prior to neoadjuvant therapy (5.9%) and 4/21 (19.0%) being evaluated with positron emission tomography as part of initial staging. There were 2 patients who had false positive findings resulting in unnecessary invasive testing. **Conclusions** In this study, Positron emission tomography imaging changed the treatment pathway in approximately 10% of patients with pancreatic ductal adenocarcinoma, primarily among patients with high risk clinical disease. The data suggests positron emission tomography imaging should be used selectively in patients with pancreatic ductal adenocarcinoma who have clinically advanced disease, where identification of distant disease would alter the patient's treatment course.

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDA) is the fourth leading cause of cancer death in the United States, with a 5 year survival of approximately 5% [1, 2, 3]. Two major factors contribute to this poor prognosis: first, PDA cells have innate resistance to chemo- and radiotherapy which render the nonsurgical options minimally effective; and secondly, a lack of early symptoms and the absence of disease-specific markers translates to less than a quarter of patients being eligible for resection at presentation [1, 4].

Given the potentially high morbidity of current therapeutic options and the aggressive nature of the disease, rapid effective staging is critical for patients with PDA. In addition to a physical exam and tumor markers, cross sectional imaging with pancreatic protocol computed tomography (CT) is the current the gold standard evaluation for PDA. CT has a diagnostic sensitivity between 85-95% according to recent studies [5, 6]. Despite this, operative staging is more sensitive where nearly 30% of patients with potentially resectable PDA are found to have unresectable disease at staging laparoscopy or laparotomy [7].

Use of PET imaging for PDA primary disease diagnosis is limited because PET cannot detect small tumors or differentiate malignancy from an inflammatory mass [8, 9, 10]. In spite of these limitations, PET has demonstrated superior sensitivity for metastatic disease in a number of other malignancies has triggered interest in applying the technology to PDA staging [11]. A number of recent studies have shown the modality to have prognostic value, with maximum fluorodeoxyglucose (FDG) uptake significantly correlating with histopathologic grade, therapeutic response, postoperative recurrence, and survival in patients with PDA [12, 13, 14, 15].

The purpose of this study was to investigate the utility impact of PET on clinical management of patients with potentially resectable disease.

MATERIALS AND METHODS

Institutional Review Board approval was obtained to evaluate patients with a diagnosis of pancreatic cancer treated at the University of Iowa. Using the University of Iowa Tumor Registry database, patients were identified who underwent PET scan performed during the course of their cancer therapy between June 2004 and May 2012. Patients were grouped into three cohorts based on the indication for PET: Group 1) patients with borderline

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resectable or locally advanced disease who received PET imaging for neoadjuvant chemoradiation planning; Group 2) patients who had PET performed prior to initiation of adjuvant chemoradiation; and Group 3) patients who received PET imaging as part of their initial staging workup. Clinicopathologic and treatment-related variables were retrospectively obtained from the medical record. The 7th Edition of the AJCC staging system was utilized [16]. Overall survival was determined from the time of diagnosis to the time of death from any cause.

The impact of PET imaging on clinical management was determined by evaluating clinical notes, prior imaging and diagnostic tests, and clinical indications for the PET scan. PET imaging is obtained as part of treatment planning for radiation therapy at our institution and therefore patients who are being considered for neoadjuvant or adjuvant radiation therapy all undergo PET/CT evaluation. This protocol is used to enhance radiation therapy treatment using focused IMRT. The patients in our study were therefore analyzed based on three clinical indications for PET/CT: Group 1 - routine evaluation prior to neoadjuvant therapy (patients with borderline resectable/locally advanced disease); Group 2 - routine evaluation prior to adjuvant therapy following pancreatectomy; and Group 3 - part of the initial staging workup. Patients were excluded if they underwent PET/CT with a known diagnosis of recurrent or metastatic disease.

PET–CT was performed using a Siemens Biograph TruePoint (Germany) system. After fasting for at least 6 hours, patients were administered 0.14 mCi/kg of fluorodeoxyglucose (FDG). 90 minutes later, whole body PET scan with IV contrast was performed from the skull to the mid-thigh.

RESULTS

62 patients identified that met inclusion criteria. The final cohort was 66.1% male with a median age of 62.5 years (range 41 – 87). AJCC clinical stage after completion of all imaging (including PET/CT) was as follows: stage I (n=6, 9.7%), stage II (n=17, 27.4%), 22 stage III (n=22, 35.4%), and stage IV (n=17, 27.4%). The clinical and demographic variables of the final cohort of 62 patients are shown in **Table 1**. Seven patients received PET as part of their evaluation for adjuvant chemoradiation (Group 1), 34 patients were being evaluated prior to neoadjuvant chemoradiation (Group 2), and 21 received PET as part of their initial staging workup (Group 3). Median length of follow up was 12.1 months (range 1.8 – 31.9 months). Survival data was available for 53 of the patients. Median overall survival was 10.3 months (range: 0.87 – 31.6 months). The remaining patients were presumed alive at time of data collection.

49 patients who received chemotherapy (79%) and 43 (69%) who received radiotherapy. Only 14 patients (22%) underwent pancreatic resection, reflecting the advanced nature of this cohort. Of the 48 patients who did not undergo resection, 25 had unresectable local disease which failed to show adequate response to neoadjuvant therapy, 13 had metastatic disease, two had poor performance status incompatible with major surgery, and 3 patients with borderline performance status declined surgery after being counseled regarding the operative risk. Five patients were found to have unresectable disease on exploratoration; four of these patients had liver metastases and one was found to have significant vascular invasion.

Median time from diagnosis of PDA to PET imaging was 1.0 months (range 0.1 - 9.8 months). In this study, sensitivity of PET was 87% and specificity was 90%.

Overall a total of six patients (9.6%) had a change in clinical management based on the results of PET imaging **(Table 2)**. Two of these patients were being evaluated for neoadjuvant chemoradiation (Group 2) and four had PET scans as part of their initial staging workup (Group 3). Five of the six patients had lesions identified on PET that were not seen on staging CT **(Figure 1)** – four of these patients were found to have liver metastasis (Group 3) and one patient had a PET-avid supraclavicular node that was positive for metastatic adenocarcinoma. One remaining patient had a highly suspicious liver lesion that was seen on CT, not amenable to biopsy, but confirmed as malignancy with PET scan. One of the newly identified liver lesions was noted as indeterminate on the initial PET scan and the patient underwent a follow up scan 3 months later to confirm the diagnosis. All of these patients had other clinical indicators of high risk disease such as a locally advanced tumor with vascular invasion or highly elevated CA 19-9. These patients were initially considered

Table 1. Clinicopathologic and Treatment Related Variables of 62 Patients with Pancreatic Ductal Adenocarcinoma.

Variable	Median (range) or N (%)
Median age, years	62.5 (41 – 87)
Male gender	41 (66.1)
AJCC stage	
I	6 (9.7)
II	17 (27.4)
III	22 (35.5)
IV	17 (27.4)
Carbohydrate Antigen 19-9 at diagnosis (U/mL)	870.2 (1 – 10,000)
Pancreatic Resection	14 (22.6)
Pancreaticoduodenectomy	10 (16.1)
Total pancreatectomy	2 (3.2)
Distal pancreatectomy	2 (3.2)
Chemotherapy	49 (79.0)
Single agent	22 (35.4)
Multi-agent	27 (43.5)
Patient refused	4 (6.4)
Radiation	43 (69.4)
External beam	15 (24.2)
Tomotherapy	13 (21.0)
Photon beam	12 (19.4)
Other/non-specified	3 (4.8)
Recommended, patient refused	2 (3.2)
Time to PET from date of diagnosis, months (range)	1.0 (0.1 – 9.8)
Median survival, months (range)	10.3 (1 – 40)

Table 2. Patients with Changes in Treatment Algorithm due to Findings on PET Imaging.

Patient	Indication for PET	Location of Critical PET Findings	Nature of Finding	Additional Clinical Indicators of High Risk for Metastatic Disease	Impact of PET Findings on Clinical Management	Survival (months)
68 M	Prior to neoadjuvant therapy	Liver metastasis	New Finding	Vascular invasion by primary tumor	Radiation withheld	40.3
70 F	Prior to neoadjuvant therapy	Liver metastasis	New Finding	Ca 19-9 = 3,300 U/mL	Radiation withheld	4.5
71 M	Initial staging	Liver metastasis	New Finding	Highly suspicious lesion on CT was PET-avid	Surgery withheld	5.6
81 F	Initial staging	Liver metastasis	New Finding	Locally advanced tumor	Radiation withheld	12.5
65 F	Initial staging	Supraclavicular lymph node	New Finding	Ca 19-9 = 2,100 U/mL	Radiation withheld	6.4
80 F	Initial Staging	Liver	New Finding	Ca 19-9 = 900 U/mL	Surgery withheld	5.7

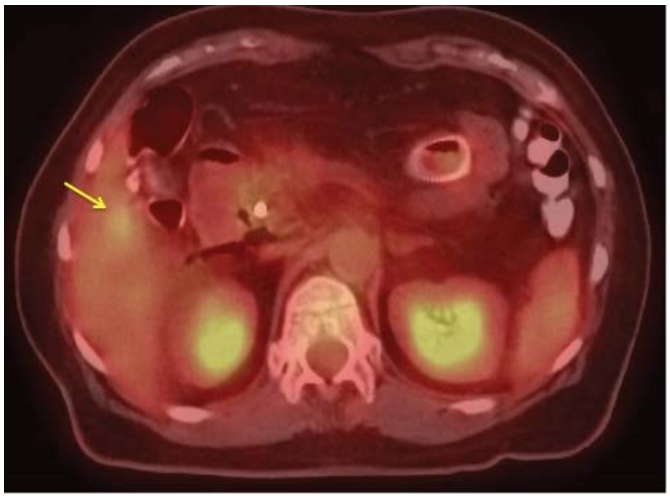

Figure 1. PET imaging of liver metastasis not seen on CT.

for radiation or resection, but PET results excluded these treatment options, all patients were treated with palliative chemotherapy.

In two patients, PET imaging resulted in unnecessary testing based on false positive results. One patient with unresectable disease underwent PET imaging prior to initiating radiotherapy. A hypermetabolic lesion was identified in his colon which was thought to represent either a primary colon cancer or pancreatic metastasis, however, follow up sigmoidoscopy revealed the lesion to be a hyperplastic polyp. The second patient was found to have an FDG-avid mass in the left maxillary sinus during initial staging. Biopsy of the sinus mass revealed a benign inverted papilloma. In both instances therapy was delayed while the new mass was evaluated.

DISCUSSION

This is a single institution retrospective review that demonstrates the treatment plan of patients with high risk PDA can be altered if stage IV disease is detected on PET.

The diagnosis of PDA carries an expected survival of approximately 18 - 24 months with localized disease, or 6 – 11 months in patients with metastatic disease [17]. Multiple studies have explored the utility of PET for staging of PDA with mixed results. PET has been shown to identify unresectable disease, but CT was able to make this determination as well, thereby rarely contributing to surgical decision making [18]. A retrospective review of 125 patients showed that PET/CT changed the surgical management in 2.6% of patients by identifying distant metastases not seen on CT [13]. A recent meta-analysis of 35 studies found the sensitivity and specificity of PET to be 90% and 76%, respectively [19]. In all the studies evaluated, CT and PET imaging were concordant in the large majority of cases [20]. In these instances, PET scanning contributes significantly to the cost of the patient's workup, without changing final clinical management [21]. Though PET is not currently recommended as part of the initial staging work-up for pancreatic cancer, its use in combination with pancreatic-protocol CT is promising. In a prospective study comparing the accuracy or PET to CT and MRI, Kauhanen *et al*. demonstrated that PET could have changed management in 26% and 11% of patients, respectively [22].

The variable results of these studies necessitates defining selection criteria for PET in order to maximize the benefit of this exam. From the current study, it is clear that patients who have clinically high risk disease and are being considered for local intervention (i.e. surgery or radiation) are most likely to benefit from the inclusion of PET in the evaluation of their treatment plan. This is consistent with the most recent NCCN guidelines, which state that PET may be utilized after obtaining a formal pancreatic protocol CT in high-risk patients to detect extrapancreatic metastasis.

Three groups of patients were evaluated in this study. Patients who had operative staging and successful resection (Group 1) were theoretically the lowest risk patients and indeed no patients had their treatment plan altered by PET imaging. Those who were being evaluated for neoadjuvant therapy (Group 2) were comprised mostly of patients being treated for locally advanced disease and PET imaging changed management in two patients (5.9%). The final group (Group 3) consisted of patients who had PET imaging as part of their initial staging. Four (19%) patients in this group had either discovery or confirmation of metastatic disease on PET imaging, suggesting that patients with borderline resectable or advanced clinical disease may be most likely to benefit from PET imaging. This subset of patients would be spared unnecessary diagnostic laparoscopy or radiation treatments. While diagnostic laparoscopy has been shown to be useful, it cannot detect isolated liver metastases deep within the liver parenchyma. These patients may undergo unnecessary formal pancreatic resection only to have

stage IV disease identified upon PET imaging obtained for radiation treatment planning. Additionally, unnecessary radiation treatment can result in morbidities including: skin changes, nausea, vomiting, diarrhea, fatigue, loss of appetite, and weight loss. Given the importance of quality of life in a disease with a short life expectancy, minimizing unnecessary surgery or radiation treatment is imperative.

Our data identified five patients with liver metastases not detectable on CT. Other studies have also demonstrated the superiority of PET imaging in detecting liver lesions [14, 23, 24]. The largest currently available meta-analysis of the utility of PET for the identification of liver metastasis showed a specificity of 96%. Similar studies of patients with less advanced disease found the positive predictive value of PET in non-concordant studies to be as low as 54%, suggesting the advanced nature of our cohort may highlight the utility of PET imaging in this population [20].

Three studies completed within the last five years that similarly attempted to evaluate the impact of PET imaging on staging and therapy planning **(Table 3)**. All studies identified a small number of cases where PET imaging prevented unnecessary surgery. In the studies, the high sensitivity of standard staging and relatively low specificity of PET findings became limiting factors. Kim *et al*. identified only two cases in 125 where PET correctly identified metastatic disease missed by standard staging modalities, despite eight instances of metastatic disease identified only at the time of surgery [25]. Pappas *et al.* evaluated 124 patients with local disease, and also identified only two cases were PET findings impacted therapy decisions [21]. The third study reported that PET imaging prevented unnecessary surgical exploration in seven of the 123 patients, however, false positives complicated the treatment of six patients [20]. The limited clinical utility identified in these studies is in contrast to similarly designed but dated trials, likely due to improved disease detection with modern CT imaging techniques [25].

It is also important to consider the limitations of this imaging modality. Non-concordant PET studies in our series had a false positive rate of 25%. The impact of false positives for suspected metastases is high in PDA. False positive results can potentially delay appropriate therapy in an aggressive disease where time is critical, trigger unnecessary and often invasive follow-up examinations, and risk inappropriately denying patients the opportunity for curative resection. While some authors portend that the cost/benefit ratio of the imaging modality may be further narrowed by the implementation of staging laparoscopy, our study demonstrates that use of PET in high risk patients could obviate the need for staging laparoscopy. These are important considerations in the clinical judgment when caring for these patients.

Despite these limitations, the use of PET imaging increased the sensitivity for metastatic disease and prevented the ineffective application of aggressive local therapy in 6 patients. It is well understood that inflammatory processes and several benign tumors can appear as false positives on PET imaging. In our series, the false positive findings were an inverted sinus papilloma, which is a locally aggressive tumor that can transform into squamous cell carcinoma, and a hyperplastic polyp in the colon [26]. Though patients with a positive PET finding in the colon are generally recommended to undergo a colonoscopy, given the aggressive nature of PDA, this evaluation may be delayed until after initial treatment of PDA. The actual impact of these false positives thereby proved to be relatively minimal in our series. The further investigation of these sorts of findings should be evaluated on a case-by-case basis.

CONCLUSIONS

The findings of this study suggest that use of PET in routine staging of PDA is of limited benefit if applied to all patients with PDA. Instead, we find that patients with clinically advanced disease, who have been deemed candidates for local therapy after a comprehensive workup may benefit the most from the utilization of PET. Reserving PET for this particular subset of patients can potentially prevent unnecessary local therapy (radiation, surgery), while minimizing the relative consequence of false positive findings that may expose patients to additional testing [27, 28]. Benefits are most likely to be seen in populations with indeterminate findings on CT or other indicators of advanced disease such that the positive predictive value may be maximized [14]. However, based on our data, patients who have been deemed resectable by conventional staging or who have undergone definitive formal pancreatic resection, PET will rarely impact patient management.

Table 3. Recent Studies Evaluating PET Imaging in Patients with Pancreatic Ductal Adenocarcinoma.

Series	n	% of patients resectable on conventional staging	% of patients with treatment altered by PET findings	% Metastatic disease identified at exploration	Key finding/suggestion
Kim, 2012(25)	125	76	2.6	10.8	PET rarely identifies new findings beyond the conventional evaluation once patients are deemed to be resection candidates
Pappas, 2013(21)	124	79	2	Not reported	The addition of PET imaging is of limited clinical utility
Einersen, 2014(20)	123	29	6.5	14	PET has higher sensitivity than CT and MRI for identifying metastatic lesions and lower specificity and positive predictive value. False positive findings can delay surgical intervention
Current Series	62	44	13	8	PET imaging is best used selectively in patients who have high risk clinical disease. Routine use of PET is not recommended

This study carries the limitation of selection bias that is inherent to all single-center retrospective reviews. Specifically, this study evaluates the practice patterns at a single tertiary care institution. The use of PET in other settings is not evaluated in this study. Additionally, another limitation is that PET was not used to assess treatment response as patients rarely underwent more than one scan. Future studies would benefit by recruiting a larger number of patients across a variety of clinical centers, and including a formal cost-benefit analysis of PET imaging in PDA staging. A prospective trial with an evaluation of the number needed to test to prevent an unnecessary resection would also advance our understanding of the application of PET for PDA therapy planning.

Conflict of Interest

The authors declare that there is no conflict of interests.

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