PET-CT in the staging of potentially resectable pancreatic cancer

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Abstract

Introduction:
Pancreatic adenocarcinoma (PDAC) presents a significant global health challenge particularly as it is generally diagnosed at an advanced stage. Although cross-sectional imaging techniques including multidetector CT (MDCT) are familiar and ubiquitously used the role and value of PET-CT scans in PDAC management remains unclear.

Methods:
This six-year study analysed patients who underwent PET-CT scans for suspected PDAC. Demographics, cross-sectional imaging and PET-CT results, management decisions, and histology were collected together with rates of operation with curative intent and the time interval between scans and surgical intervention.

Results:
Among 161 patients, 110 were operable with curative intent but in 51 no surgical intervention was appropriate or possible. Among patients considered operable, 20 had extra pancreatic PET avid lesions while 90 did not. Among those without extra-pancreatic lesions, 68 underwent surgical exploration, 12 were unfit for surgery, and 10 had inflammatory or benign conditions. In the group who underwent surgical exploration, 9 patients were found to have suspected metastasis prior to their PET scans which were not confirmed on subsequent PET-CT scans. Considering all patients who underwent an exploratory laparotomy 48 underwent successful resection and 20 were found to have disease which precluded potentially curative surgery. In the subset of patients with extra-pancreatic lesions, 4 were inoperable due to the demonstration of unequivocal metastasis on PET-CT but the remaining 16 patients underwent surgical exploration when the decision of the HPB MDT was that lesions were equivocal or may be unrelated to the primary pathology. Of these 16 patients, 9 were resectable and 7 were unresectable and PET-CT scans influenced the management of patients in 8% of cases. The median interval between MDCT and PET-CT scans was 27 days with an average of 36.7 days. The median duration between MDT and PET-CT scans was 12.5 days with an average of 20.2 days.

Conclusion:
PET-CT scans play a crucial role in the management of suspected PDAC, but routine use may not be justified. Further research is needed to identify the subset of patients who benefit most. Clear guidelines for PET scan utilization in clinical practice are required to optimize the role in PDAC management.

Introduction
Pancreatic adenocarcinoma (PDAC) continues to be a major public health issue, accounting for almost 5% of cancer-related deaths globally and ranking fourth with regards to cancer mortality rates within the European Union [1, 2]. The prognosis remains dismal with less than 5% of patients alive after five years largely due to its insidious onset, consequent delayed and late diagnosis, aggressive biological behaviour nature and propensity for early systemic spread [3]. Although surgery offers the only chance for a cure in PDAC patients, it is feasible in only 15–20% of cases following presentation [4]. Identifying and staging PDAC as early and as precisely as possible is crucial since it enables potentially curative resection in carefully selected patients. The mainstay of diagnosing and staging PAC, as well as identifying patients who will benefit from radical treatment, remains cross-sectional imaging.
Multiple imaging techniques have been described and employed in diagnosing and staging PDAC and thin-section Multidetector CT (MDCT) scans remains the most commonly utilised [5, 6]. Its ubiquitous availability and accessibility, high sensitivity and specificity, and ability for images to be assessed pre-operative by surgeons means it remains the preferred imaging modality [7]. Although magnetic resonance imaging (MRI) has demonstrated comparable sensitivity and specificity as it remains not as widely available and is susceptibility to motion artefacts and patient intolerance it is generally used as a problem-solving tool for inconclusive MDCT scans [8, 10]. Positron emission tomography (PET) is a relatively recent innovation which rapidly became popular in oncological specialities and in HPB surgery was adopted for the investigation, assessment and staging of patients with suspected PDAC.

The use of PET scan in the assessment of patients with pancreatic adenocarcinoma (PDAC) is not uniformly incorporated in clinical practice guidelines. Neither the National Comprehensive Cancer Network (NCCN) nor the European Society for Medical Oncology (ESMO) currently recommend the routine use of PET scan for either the diagnosis or staging of PDAC [11, 12]. Similarly, the 2020 published guidelines of the Italian Association of Medical Oncology (AIOM) do not recommend the use of PET scan in PDAC [13] although in contrast, the 2019 Clinical Practice Guidelines for Pancreatic Cancer from the Japan Pancreas Society recommend the use of PET scan in all cases of suspected distant metastasis, although the strength of recommendation is weak [14].

In December 2018, the National Institute for Health and Care Excellence (NICE) published guidelines outlining the diagnostic and management approach to pancreatic cancer. NICE guidelines recommend the use of PET scan for all adult patients with localised pancreatic cancer prior to offering curative interventions such as surgery, radiotherapy, or systemic chemotherapy. The primary objective of this recommendation is to improve the detection rate for distant metastases, as putative curative interventions in such patients might negatively affect their quality of life without significantly improving their life expectancy [15].

The guidelines suggest that the precise role of PET scans has not been firmly established, and there are concerns among both oncologists and surgeons about its use in patients with initially resectable pancreatic adenocarcinoma specially as to whether it should affect the management. This study aims to assess the influence of PET scans on the management of PDAC patients in our unit.

Methods

This study included all patients who underwent PET-CT scans for suspected pancreatic adenocarcinoma. The cohort was identified using the Hepatobiliary and Pancreatic (HPB) surgery unit database at the University Hospital of Leicester NHS trust, which recorded patient referrals to the HPB Multi-Disciplinary Team (MDT) meeting over a six-year period (2015–2021). Patients with pancreatic lesions in the head of the pancreas (HOP) or body/tail lesions were included, and an additional filter applied to identify those who had undergone PET-CT scans.

Demographic information for the selected cohort was recorded in a Microsoft Excel spreadsheet after obtaining the necessary local approvals. The date each patient was referred to the HPB MDT and the date of the first MDT meeting in which they were discussed, and management plans decided was recorded. The radiological scans patients underwent, including MDCT scans, MRI, and PET-CT scans, were recorded using EMRAD PACS, a radiology scan reporting software. The date and findings of each scan, including details of the location and extent of the primary lesion and any identified or potential metastatic disease were recorded, focussing on PET-CT scans and any newly discovered extra pancreatic or metastatic lesions that would influence further management. Additional patient outcomes and MDT meeting details were obtained from the SOMERSET cancer register software together with the final histology of each tumour via the pathology and histology reporting software ICE.

The cohorts of patients with operable or inoperable disease were identified, and the stage at which they were deemed inoperable (initial MDT meeting, following surgical exploration, or following PET-CT scan) recorded. The median and
average time between each radiology scan performed was calculated together with the time taken to surgical intervention from the date of the initial MDT discussion.

Results

A total of 161 patients who had undergone PET-CT scan for suspected PDAC were included in the study. Among them, 110 were found to have operable disease, while 51 were deemed to have inoperable disease. Among the patients with operable disease, 85 had lesions in the head of the pancreas, while 25 had lesions in the body/tail. Of the 85 patients with HOP lesions, 61 underwent surgical exploration, and for the 25 patients with body/tail lesions, 23 underwent surgical exploration. Among the 51 patients initially deemed to have inoperable disease, 42 had lesions in the head of the pancreas, and 9 in the body/tail (Fig. 1).

Among the initial 110 patients considered operable following discussion at the MDT, 20 patients were discovered to have extra pancreatic PET avid lesions while the remaining 90 patients had no evidence of additional disease. Within the group with no demonstrable extra pancreatic PET avid lesions, 68 underwent surgical exploration, 12 were deemed unfit for surgery and 10 were diagnosed with inflammatory or benign conditions. Of the 68 patients who underwent surgical exploration, 9 patients were found to have suspected metastasis on imaging prior to their PET scan, but these findings were not supported by the subsequent PET-CT scan. During surgical exploration, 48 patients underwent successful resection, while 20 patients were found to be unresectable.

In the group found to have extra pancreatic avid lesions at presentation, 4 patients were found to have significant metastatic disease on the PET-CT scan, rendering them inoperable. Among the group of patients displaying extra pancreatic PET avid lesions, the MDT concluded that in 16 cases these findings were unrelated or equivocal and the MDT recommended surgical exploration with potentially curative intent following assessment of the equivocal lesions demonstrated on PET-CT. At exploration in this cohort 9 individuals were found to be resectable, while 7 patients were deemed unresectable. The PET-CT scan has changed the management in a total of 13 patients in our cohort which represent 8% of total cases (Figure 2).

The average and median duration in days between MDCT, MDT, and PET-CT scans were also calculated. The median interval between the MDCT and PET-CT scans was 27 days, while the average was 36.7 days and the median duration between the MDT and PET-CT scans was 12.5 days, with a median of 20.2 days (Table 1)

<table>
<thead>
<tr>
<th></th>
<th>CT – PET</th>
<th>MDT – PET</th>
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<tbody>
<tr>
<td>Median</td>
<td>27</td>
<td>12.5</td>
</tr>
<tr>
<td>Average</td>
<td>36.7</td>
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Discussion

The PET scan relies on the fact that tumour cells exhibit a significantly higher rate of glycolysis [16]. The most commonly used tracer in PET scans is 18F-fluorodeoxyglucose (18F-FDG), which is involved in glucose metabolism and accumulates in tumour cells. In 1999, PET was combined with CT scan to add anatomical information to functional images [17]. Since this innovation PET-CT scanning has become an integral part of the oncological armamentarium and is used for the diagnosis and staging of a wide range of disparate cancers, and has been incorporated into international guidelines [18], [19]. Despite the increasing experience with a number of cancers there remains a paucity of data identifying its utility in the assessment and management of patients with PDAC.
Two meta-analyses have failed to demonstrate that the use of PET-CT scan in diagnosing PDAC is superior to MDCT. They concluded that despite the sensitivity of 90% and specificity of 76% the higher cost, impact on delaying the management pathway and radiation risk precludes recommending the routine use of PET-CT scan over MDCT scan [20], [21]. Nevertheless, it remains clear that to determine in which patients potentially curative treatment is appropriate staging is of paramount importance. Before considering therapeutic treatment it is mandatory to investigate loco-regional lymph nodes to identify involvement where possible and exclude distant metastasis [22]–[24]. Although a positive local lymph node does not always mean that a potentially curative resection is possible if the node(s) would be resected en-bloc with the PDAC it is a crucial prognostic marker [25]. PET-CT scan has shown inferior results in detecting lymph nodes involvement, with detection rates ranging from 21%-38%, while MDCT scan has demonstrated clear superiority in this aspect [26, 27].

The usefulness of PET-CT scans in managing pancreatic adenocarcinoma lies primarily in its ability to rule out distant metastasis. PET-CT scanning has been shown to have higher sensitivity for the detection of lung and bone metastases reported as high as 100% [28]. PET-CT also has the advantage because of being a whole body scan of being able to detect metastases in unusual sites and those where MDCT is less able to be dogmatic such as the ovarian and peritoneum particularly for the latter where there has been previous abdominal surgery [29]. However, when it comes to detecting liver metastasis, PET-CT has been found to have a very variable sensitivity with reported rates ranging from 22–88% [26, 28, 30, 34]. This lower sensitivity compared with the potential for the detection of lung and bone metastases, may be due to the higher metabolic background of the liver, especially in cases of small size metastasis [35]. Several studies have compared PET-CT scans with MDCT for the detection of liver metastases and although the sensitivity of PET-CT was higher than MDCT in this respect this was not statistically significant [20, 27, 31, 33].

Although the sensitivity of PET-CT scans has been compared to other imaging modalities, the important question is whether its routine use would influence the clinical management of patients with PDAC. Some studies have demonstrated that the use of PET-CT scanning influencing management in a significant proportion of patients. This includes the PET-PANC study where 20% of patients had their proposed surgical resection abandoned [36]. This is not however a consistent finding and other studies have reported a more modest impact on management. In our study 8% of patients in our unit being considered for surgical resection had their management changed by PET-CT scans, primarily due to the detection of new metastases that precluded surgery, or by the clarification of a suspicious lesion(s) detected by MDCT scan. Another concern identified in a number of studies is the potential delay introduced in managing this time-critical disease [37]. In our cohort, MDCT scans were typically performed prior to the first MDT discussion, with PET-CT scans requested by the MDT. There was an average delay of 20 days between the MDT and PET-CT scan and although it is difficult in all cases to attribute all of the delay to the decision to request a PET-CT scan, it certainly contributed to it in all cases.

Neoadjuvant chemotherapy is becoming increasingly popular in a number of HPB units managing PDAC patients and in many it is now considered the treatment of choice for borderline resectable tumours and in an increasing number of units for PDAC tumours resectable at presentation [38, 39]. After completion of chemotherapy, these patients need to be reassessed to see if they are suitable for exploration with curative intent which can be challenging due to the ubiquitous desmoplastic reaction and fibrosis produced by chemotherapy and PDAC which is very difficult to distinguish from tumour tissue [40]. According to the NCCN guidelines the majority of lesions still demonstrate stability on MDCT scans after neoadjuvant chemotherapy making it an imperfect tool for assessment and staging following upfront treatment [11]. This contrasts with the utility of PET-CT scanning which has been shown to be very valuable in this cohort of patients when assessing resectability [41]. The authors believe that there are significant advantages to the routine use of PET-CT scan in the assessment of PDAC following neoadjuvant chemotherapy, and that it should be incorporated into the guidelines across UK and Europe.

In conclusion PET-CT scanning continues to play an important role in the assessment and management of patients with suspected PDAC. Routine use however may not be justified, and additional research is necessary to determine the subset of patients with PDAC at initial presentation who will benefit from the use of PET-CT scanning. The situation is clearer for the
assessment of patient initially treated with chemotherapy +/- radiotherapy because of the difficulty of differentiating between the desmoplastic response and residual tumour with MDCT. Research efforts need to be directed towards high quality studies which will enable clear guidelines for the use of PET scans in clinical practice to be established.

Declarations

**Conflicts of interest declaration.** The authors declare that they have no conflicts of interest related to this research.

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**Authors Contribution.** Tareq Al saoudi, John Isherwood and Giuseppe Garcea contributed to the conception, design, data analysis, interpretation of results, and writing of the manuscript. Kanika Chawla and Dawud Sarwar contributed to data collection and writing the method and result section. All authors have read and approved the final version of the manuscript and take full responsibility for the accuracy and integrity of the work.

References


Figures

Figure 1

161 Patients who had PET for Pancreatic lesions

130 Operable

85 HLP lesion

41 underwent surgical exploration

24 No surgical exploration

25 body/tail lesion

51 Non-Operable

42 HLP lesion

9 body/tail lesion

7 No surgical exploration

Figure 1
Characteristics of the patients who had PET-CT scan for pancreatic lesions

**Figure 2**

Characteristics of patients who found initially operable by MDT

- 110 Operable on initial assessment
  - 90 No Extra Pancreatic PET avid Lesions
    - 68 Underwent Surgical exploration
    - 12 Unfit for Surgical exploration
    - 10 inflammatory / benign
  - 20 Extra Pancreatic PET avid lesions
    - 4 PET revealed Metastatic disease
      - 48 Resectable upon exploration
      - 20 Unresectable
      - 16 found insignificant
  - 9 Resectable upon exploration
  - 7 Unresectable

Pre-PET MDCT scan showed suspected metastasis in 9 Patients