PET-PANC: multicentre prospective diagnostic accuracy and health economic analysis study of the impact of combined modality ^{18}fluorine-2-fluoro-2-deoxy-D-glucose positron emission tomography with computed tomography scanning in the diagnosis and management of pancreatic cancer

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Scientific summary

The PET-PANC study

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Scientific summary

Background

Pancreatic cancer is one of the major causes of cancer death. In the UK population in 2011 the incidence of pancreatic cancer was 8773 (15.7 per 100,000 in 2012) and in 2012 there were 8662 deaths from pancreatic cancer. The 5-year survival rate for all patients with pancreatic cancer persists at 7%. Median survival for patients with advanced disease is between 3 and 6 months; this can be improved with chemotherapy. The 5-year survival rate is 10–15% following surgical resection and increases to 20–30% with adjuvant chemotherapy. Pancreatic cancer diagnosis is challenging and patients may be relatively asymptomatic during its early course. Standard diagnostic practice consists of contrast-enhanced multidetector computed tomography (MDCT), endoluminal ultrasound (EUS) and magnetic resonance imaging (MRI) for equivocal liver lesions. There are up to 10–20% of patients in whom an accurate diagnosis is difficult. Combined positron emission tomography and computed tomography (PET/CT) adds precise anatomical localisation to functional data. The use of PET/CT may add further value to the diagnosis and staging of pancreatic cancer.

Objectives

The primary objective was to determine the incremental diagnostic accuracy and impact of PET/CT in addition to standard diagnostic work-up in patients with suspected pancreatic cancer. Secondary objectives were to (1) evaluate changes in diagnosis, staging and patient management through the addition of PET/CT; (2) determine the cost-effectiveness of the addition of PET/CT in the diagnosis, staging and management of pancreatic cancer; (3) evaluate the impact of PET/CT in chronic pancreatitis; (4) identify which groups of patients would most benefit from PET/CT; and (5) report the incremental diagnostic value of PET/CT for particular types of pancreatic tumour.

Methods

Design and interventions

This study was a multicentre prospective diagnostic accuracy and clinical value study of PET/CT in suspected pancreatic malignancy. Following standard diagnosis and staging with MDCT, eligible patients underwent PET/CT within 2 weeks of informed consent. All PET/CT scans were centrally reviewed. Diagnosis, staging and planned management were recorded before (D1) and after (D2) PET/CT. Actual diagnosis, staging and management were then recorded (D3). The reference standard (D4) was based on histology or clinical outcome after 12 months' follow-up.

Setting

The study took place in 18 UK pancreatic tertiary referral centres.

Participants

Patients with suspected pancreatic malignancy defined as one or more of (1) focal lesion in the pancreas/bulky pancreas/dilated pancreatic duct (± metastases) detected on MDCT scan (± MRI/EUS/ultrasound); (2) jaundice due to distal obstruction (not due to calculi) defined as serum bilirubin > 35 µmol/l; and (3) serum carbohydrate antigen 19-9 (CA19.9) > 37 kU/l.

Sample size

A previous meta-analysis reported a sensitivity of 81% and specificity of 66% for the diagnosis of pancreatic cancer with standard MDCT. The primary objective of this study was to investigate the incremental value of PET/CT. To be of clinical value to the diagnostic work-up the addition of PET/CT should increase sensitivity from 81% to 90% and specificity from 66% to 80%. Using methodology for a paired design, the number of diseased and non-diseased subjects required to have 80% power to detect these differences at the 5% (two-sided) significance level ranges between 87 and 281 (diseased) and 57 and 221 (non-diseased) depending on the assumption made about the correlation between the test errors (false positives and false negatives). To ensure adequate power, the largest of these (281 diseased patients = 600 pancreatic cancer patients assuming 47% prevalence) was the initial target for recruitment. An interim analysis was carried out after 200 patients were recruited and the reference standard obtained. The sample size was then revised down to 500 patients.

Follow-up

All patients were followed up after consent for 12 months or until death if before 12 months. The follow-up consisted of 3-monthly clinic visits and data collection as standard for the diagnosis and that centre.

Outcome measures

The primary outcome measure was incremental diagnostic value (sensitivity and specificity) of PET/CT in addition to standard diagnostic work-up with MDCT. The secondary outcome measures included (1) changes in patients' diagnosis, staging and management as a result of the addition of PET/CT; (2) changes in the costs of patient management as a result of the addition of PET/CT and effectiveness measured in terms of survival and/or health-related quality of life; (3) incremental diagnostic value of PET/CT findings in chronic pancreatitis; (4) identification of groups of patients who would benefit the most from PET/CT based on clinical outcome; and (5) incremental diagnostic value of PET/CT findings in other pancreatic tumours.

Statistical methods

The analysis focused on investigating incremental diagnostic accuracy and incremental diagnostic impact. Diagnostic accuracy was investigated by comparing the baseline diagnosis (D1) and the results of the PET/CT scan with the reference diagnosis (D4); diagnostic impact was investigated by comparing the baseline (D1) and post (D2) PET/CT diagnoses with the reference diagnosis (D4). The diagnostic impact of standard work-up was estimated by comparing diagnostic decisions made at D1 with the reference diagnosis made at D4 and expressing as sensitivities and specificities together with 95% confidence intervals (CIs) (computed using binomial exact methods). To evaluate the accuracy of staging by standard work-up the analysis was restricted to individuals with pancreatic malignancy diagnosed at the reference diagnosis. The accuracy of the revised diagnoses made after PET/CT was assessed in the same way making comparisons between diagnostic and staging decisions made at D2 and the final reference diagnosis.

The initial analysis of the incremental benefit of PET/CT over standard work-up was assessed through comparing the sensitivity and specificity of diagnostic decisions D1 and D2 in both absolute and relative terms. Tabulations were created of cross-classifications of the D1 and D2 diagnoses for diseased and non-diseased patients to investigate the within-patient changes induced by the PET/CT scan with their significance assessed using McNemar's test for paired data. Subgroup analyses using generalised estimating equation (GEE) regression modelling (taking account of paired data) were undertaken to investigate whether test performance varied according to presenting conditions. The incremental accuracy of PET/CT over standard work-up was investigated using regression modelling following the Knottnerus approach. Further paired analysis was undertaken in a similar manner to investigate whether or not PET/CT introduced changes to patient management plans and the levels of confidence associated with diagnostic decisions.

Quality assurance of the positron emission tomography and computed tomography scans

A PET/CT Core Laboratory facility was set up as part of the National Cancer Research Institute (NCRI) PET Research Network. PET/CT data were transferred in anonymised DICOM (Digital Imaging and

Communications in Medicine) part 10 format. The laboratory ensured that images acquired from participating centres were of comparable quality.

Health economics

Health economic analysis was conducted from a NHS perspective. Our cost-effectiveness analysis was in three parts: model 1, in which we calculated the marginal cost per additional correct diagnosis of pancreatic ductal adenocarcinoma (PDAC) using PET/CT and CT alone; model 2, in which we calculated the budget impact of use of PET/CT; and model 3, in which we modelled the change in management of patients as a result of use of PET/CT in diagnosis over a 1-year time horizon. We undertook sensitivity analysis to explore uncertainty in costs (univariate) and model structure (structural). Probabilistic sensitivity analysis assessed the likelihood that PET/CT is cost-effective at £20,000 per quality-adjusted life-year (QALY) and £30,000 per QALY thresholds.

Results

Between January 2011 and April 2013 589 patients with suspected pancreatic cancer underwent MDCT and PET/CT in 18 UK pancreatic centres, of whom 550 patients had complete diagnostic data (D1–D4) and in range PET/CT (per protocol). In total, 261 patients (47%) had PDAC and 216 patients underwent resection.

For the diagnosis of pancreatic cancer, the sensitivity and specificity of MDCT and PET/CT were 88.5% and 70.6% and 92.7% and 75.8%, respectively. The median maximum standardised uptake value ($SUV_{max.}$) was higher for patients who were confirmed to have pancreatic cancer than for patients who did not have pancreatic cancer (7.5 vs. 5.7, respectively; $p < 0.0001$). PET/CT demonstrated a significant improvement in relative sensitivity ($p = 0.01$) and specificity ($p = 0.023$) compared with MDCT. Incremental likelihood ratios demonstrated that the results of the PET/CT significantly improved diagnostic accuracy in all scenarios ($p < 0.0002$). PET/CT correctly changed the staging of pancreatic cancer in 56 (10%) patients ($p = 0.001$); this was for stage IIb and IV. The PET/CT scan was perceived to have influenced the planned management in 250 (45%) patients. A significantly higher proportion of patients (11% vs. 4%; $p = 0.0002$) followed the management plan recommended after PET/CT (and not that recommended after MDCT) than the MDCT management plan (and not that recommended after PET/CT). The most common change was from resection to no resection, which occurred in 60 patients, representing 11% of all patients and 21% of patients scheduled for some kind of resection after MDCT. PET/CT stopped resection in 58 (20%) patients who were due to have surgery.

For the diagnosis of chronic pancreatitis the sensitivity and specificity of MDCT and PET/CT were 36.6% and 98.4% and 46.3% and 98.4%, respectively. GEE subgroup analysis comparing the patients within range for both uptake time and blood glucose level with those out of range for either showed a statistically significant deterioration in sensitivity among out-of-range patients of 52.9% ($p < 0.0001$). The sensitivities and specificities of MDCT and PET/CT for the diagnoses of (1) malignant cystic neoplasm, (2) cholangiocarcinoma, (3) neuroendocrine tumour and (4) periampullary tumour were (i) 75% and 92.8% and 75% and 96.1%, (ii) 25% and 97.8% and 25% and 98.8%, (iii) 44.4% and 99.4% and 44.4% and 98.7% and (iv) 71.1% and 95.9% and 65.8% and 97.2%, respectively. The sensitivity and specificity of MDCT and PET/CT for the diagnoses of malignancy compared with benign disease were 97.4% and 47.0% and 97.7% and 68.7%, respectively. The 6- and 12-month survival rates for the overall patient population were 82.8% (95% CI 79.7% to 86.0%) and 69.0% (95% CI 65.1% to 73.1%), respectively. Patients who had a diagnosis of pancreatic cancer had 6- and 12-month survival rates of 71.4% (95% CI 66.0% to 77.2%) and 50.9% (95% CI 44.9% to 57.6%), respectively.

The cost of PET/CT differed according to the type of department the cost was sourced from within the published NHS reference costs. In 2012–13 this was £795 per scan for the nuclear medicine department and £563 for the clinical oncology department. Nuclear medicine was chosen as the most conservative cost for the base case. Model 1 in the health economic analysis demonstrated that the incremental cost per

additional accurate diagnosis was £15,309 (95% CI £15,072 to £15,460). Model 2 showed a budget impact of £6.2M per year if 100% of newly diagnosed patients received PET/CT. Model 3 demonstrated that, in the base case, the incremental cost of PET/CT was –£645 (95% CI –£2743 to £1314). The mean QALY gain associated with PET/CT was 0.0157 (95% CI –0.0101 to 0.0430). PET/CT dominated MDCT as PET/CT was both less costly and more effective. The lowest cost and highest QALY gain were seen for the PDAC with resection group. Sensitivity analysis of the cost of PET/CT using increased costs savings was performed. The cost saving was £912 per patient when we took our estimate from the clinical oncology department. Structural sensitivity analysis involved varying our base-case assumption that all patients received a resection. Some patients received bypass or open and shut laparotomy. For this model the incremental cost of PET/CT was estimated as £419 (95% CI –£138 to £930) and the mean QALY gain associated with PET/CT was 0.0078 (95% CI –0.0012 to 0.0172), resulting in an incremental cost-effectiveness ratio (ICER) of £53,777 per QALY gained. The probability of PET/CT being cost-effective at a National Institute for Health and Care Excellence (NICE) threshold of £20,000 per QALY was 18% and at a threshold of £30,000 per QALY was 28%. It should be remembered that overall QALY gains were small and so any change in costs had a big impact on the ICER. Using clinical oncology costs within this model, the ICER was £19,445 per QALY, which is cost-effective at the lower NICE threshold of £20,000 per QALY. For this combination of model and costs, the probability of cost-effectiveness at a £20,000 per QALY threshold was 50%, rising to 60% at the upper threshold. Of note, the most cost-effective subgroup was the PDAC with resection subgroup, with ICERs of £4626 per QALY and £34,654 per QALY for the clinical oncology and nuclear medicine departments as sources of costs, respectively. Overall, our base-case analysis showed that PET/CT dominated MDCT alone, in particular for patients suspected of having pancreatic cancer after standard diagnostic work-up and who were planned for surgery. The QALY gains were small and our analysis was sensitive to our source of published costs and to structural assumptions in the model.

Conclusions

This is the first multicentre, prospective, large-scale study of PET/CT in the diagnosis and management of patients with suspected pancreatic cancer. PET/CT demonstrated significantly increased relative sensitivity and specificity compared with MDCT and provided significant incremental diagnostic benefit in addition to MDCT in the diagnosis of pancreatic cancer. PET/CT altered the staging of pancreatic cancer in a significant proportion of patients. PET/CT influenced management in 45% of patients and prevented potentially futile resection in 20% of patients scheduled for surgery. PET/CT had limited use in chronic pancreatitis and other pancreatic tumours. It is likely that PET/CT will be cost-effective for patients with suspected pancreatic cancer at current reimbursement rates for PET/CT to the UK NHS.

Implications for health care

This study was designed to evaluate the diagnostic accuracy of PET/CT and its effects on management and cost-effectiveness in patients with suspected pancreatic cancer in a prospective, multicentre manner. Based on the evidence from the study, PET/CT adds significant benefit to patients in terms of diagnosis, staging and management of pancreatic cancer. The most cost-effective use of PET/CT was in the subgroup of patients who were suspected of having pancreatic cancer on MDCT and who were planned for surgery. The evidence was limited on the use of PET/CT in patients with chronic pancreatitis, other pancreatic tumours and pancreatic cysts.

Recommendations for future research

The role of PET/CT in the diagnosis and management of intraductal papillary mucinous neoplasm deserves further evaluation. The role of alternative radiopharmaceuticals for PET/CT should be assessed in terms of the diagnosis and prognosis of pancreatic cancer. The role of PET/CT as a response marker in the treatment of pancreatic cancer needs to be evaluated. More data are needed on the prognosis of MDCT-alone patients: (1) scrutiny of how patients fare with MDCT alone (PET/CT is not available; these data would be useful for future economic modelling exercises); (2) extrapolation of what happens to patients beyond the 12-month follow-up (resources were not available for us to do so in this study); and (3) stronger data on unnecessary surgery to add to the strength of the conclusions.

Study registration

This study is registered as ISRCTN73852054 and UKCRN 8166.

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