REVIEW ARTICLE

The current role of PET-CT in the characterization of hepatobiliary malignancies

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Abstract

Background: Surgery has become heavily dependent on accurate imaging in the assessment and treatment of suspected or confirmed intra-abdominal malignancy. Positron emission tomography-computed tomography (PET-CT) fuses uptake of a radiotracer combined with CT images to assess both functional tissue activity and anatomical detail. Since its introduction it has offered new ways of treating gastrointestinal cancers.

Methods: The review analyses the present literature regarding the use of PET-CT in the assessment, diagnosis, staging and treatment of hepatobiliary malignancies.

Results: PET-CT is widely used in pre-operative tumours staging for colorectal liver metastases. There is convincing data that it may also be applicable for neuroendocrine tumours, assessment of indeterminate pancreas lesions and clinical drug trials. PET-CT is of limited value in hepatocellular cancers, although new techniques in dual-tracer PET-CT may change this.

Conclusion: Knowledge of the strengths and limitations of PET-CT is important for all surgeons managing cancer of the hepatobiliary system. More clinical data are required on PET-CT, particularly its effect on long-term survival in PET-CT-staged patients undergoing resection.

Keywords
PET/CT, CT/PET, colorectal cancer, colorectal hepatic metastases, hepatocellular cancer, pancreatic cancer, cholangiocarcinoma, gallbladder cancer, neuroendocrine, cyst

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Introduction

Surgery has become heavily dependent on accurate imaging in the assessment and treatment of suspected or confirmed intra-abdominal malignancy. The role of cross-sectional imaging in this context can be multiple and includes the diagnosis of malignancy, staging of confirmed cancers, assessment of response to treatment, planning of neoadjuvant treatment (such as radiotherapy) and surveillance both pre- and post-operatively (Fig. 1). Unlike conventional imaging, positron emission tomography (PET) combined with computed tomography (CT) (PET-CT) allows an evaluation of the physiological and biochemical processes underlying malignant disease and consequently offers a new perspective in the treatment of intra-abdominal malignancies. The majority of the literature regarding PET-CT is published in radiological journals; however, surgeons as one of the main clients of cross-sectional imaging must be familiar with the concepts, strengths and weaknesses of advances such as PET-CT. The focus of this review will be to update the reader regarding the current evidence of how PET-CT is employed in the management of hepatobiliary cancers.

Positron emission tomography

Positron emission tomography is based on detecting positrons released by radiopharmaceuticals, known as tracers. A positron is a positively charged particle emitted from a parent nucleus. These tracers are bound to molecules which are involved in normal or pathological processes. The uptake of these functional molecules (known as probes) can then be detected and quantified. The first PET scans were reported in the 1980s and since then, their use in
both research and practical applications has rapidly expanded.\textsuperscript{1} The most widely used molecule is \textsuperscript{18}Flurodeoxyglucose (\textsuperscript{18}F-FDG) which is a glucose analogue actively transported into all living cells. After intra-cellular transportation and phosphorylation, \textsuperscript{18}F-FDG is locked within the cell, as (unlike glucose) it is unable to undergo further metabolism. Cellular uptake of \textsuperscript{18}F-FDG is related to expression of glucose transport membranes within the cell membrane. These proteins are expressed in all cells but are over-expressed in malignant tissue leading to intracellular accumulation of \textsuperscript{18}F-FDG which can be visualized\textsuperscript{2} using a gamma camera (Fig. 2). Other tissues such as brown fat, skeletal muscle and inflamed tissue also demonstrate increased uptake of \textsuperscript{18}F-FDG\textsuperscript{3} and may lead to false-positive results. Depending on the focus of investigation, other probes can be employed, for example \textsuperscript{18}F-fluoride is used for PET scans where measurement of increased bone activity (for the detection of bony metastases) is required.\textsuperscript{4}

**PET-CT fusion**

The combination of conventional cross-sectional imaging with PET scanning enables both functional and anatomical information regarding a patient to be fused into one study. With PET images in isolation, it may be impossible to accurately localize an area of increased activity as a result of the absence of identifiable anatomical structures. With a normal CT scan, the intensity of the images seen correlates with the structure and visceral density of the examined organ. However, in PET-CT the image intensity is dependent on the functional activity of the tissue taking up the radiotracer. In addition to PET-CT, other promising fusion imaging includes single-photon emission tomography (SPET) or PET/magnetic resonance imaging (MRI). SPET is similar to PET-CT with the main difference being the utilization of radiopharmaceutical agent employed; SPET employing gamma ray-emitting tracers which are detected by a gamma camera. In addition to improving the clarity of images, PET-CT fusion offers other advantages including a shorter scan time (by reducing the period required to correct for changes in tissue electron density) leading to increased patient
throughput and reducing the amount of radiotracer used, thereby reducing the imaging cost per patient.5,6

Special considerations in PET-CT

The advent of PET-CT fusion has required modifications to CT and PET protocols in order to achieve clarity and precise overlap of images. Contrast material artefacts are possible, particularly in thoracic veins, and as a consequence some centres will employ a caudocranial image acquisition protocol rather than the traditional craniocaudal sequence.7 Alternatively, a saline flush is administered after contrast injection.7 Full-body PET-CT images will typically only cover from the head to the upper thighs, especially when used in the investigation of abdominal malignancies. For melanomas and soft tissue tumours, the lower limbs will be included in the imaging protocol. Intense tracer uptake within the brain limits the usefulness of PET scanning in detecting cerebral abnormalities and for this reason the CT component of the images may be of greater diagnostic value.

Shallow breathing is generally permitted during both PET and CT image acquisition. However, this may lead to problems in accurate image co-registration. Fusion of images has been shown to be most accurate if the CT is acquired during normal expiration and this would be the goal in ‘whole-body’ CT scans but may be difficult to achieve. Breathing during scanning of the lower lungs and upper abdominal viscera may be an adequate compromise. For small pulmonary lesions, particularly if located around the diaphragm, breathing artefacts may hamper lesion detection. Additional low-dose CT, during maximum inspiration or expiration, may be included after the standard PET-CT to improve image clarity.7 However, this is at increased radiation exposure, and there is no current consensus of opinion on the adoption of such techniques.

After 18F-FDG administration, patient activity is limited for up to 20 min afterwards to avoid excessive uptake of tracer into skeletal tissue.9 Accumulation of tracer in the bladder may hamper accurate visualization of pelvic organs and patients are encouraged to void prior to their scan, some centres may also employ catheterization, although this is not routine practice.9 Intravenous and oral contrast can be used to optimize the diagnostic accuracy of the CT component of the scan. Scanning times will inevitably vary according to the model of scanner and the scanning protocol used. On average, CT studies will take about 60 to 70 s and the PET component 30 to 45 min.9

Standardized uptake value (SUV) is a semi-quantitative assessment of tracer uptake from the PET image. SUV from normal tissue is predictably less than that of malignant lesions. Base-line SUV is a useful measurement when using PET-CT to monitor tumour response to treatment. A decrease in SUV can be correlated with reduced physiological activity within a cancer, thus corresponding to response to treatment.9 As SUV can vary according to the time from tracer injection to image acquisition, standardization of this is important.10

Research applications of PET-CT

PET-CT, as yet, has a small role in the drug development; however, it has shown considerable promise in its applicability to assess drug metabolism, distribution and tumour response to new compounds. At present, the bulk of the literature describes PET in isolation, but with the increasing number of PET-CT scanners, particularly in clinical practice, it seems likely that fusion images will also be employed in the future. Utilization of PET in drug trials has been largely confined to human clinical trials, but in small animal models PET has also been employed. The resolution of scanners used in pre-clinical animal trials is of necessity greater than those used in a clinical setting (by up to four-fold). PET-CT has several potential advantages over conventional assessment of tumour response to treatment in murine models, as the CT component can be used to measure tumour size and the PET scan can correlate changes in size with reduction in tumour activity. CT has been shown to be more accurate than standard measurements in assessing tumour size11 but this increased accuracy is gained at a greater cost than conventional calliper measurement. PET alone has been used in a number of animal models to measure immune response, tumour hypoxia and gene expression after experimental treatment.12–14

Patient selection for drug trials

Many novel anti-tumour agents specifically target cell surface receptors, the expression of which may vary between individuals. Patients with a low receptor expression are unlikely to benefit from such novel agents and hence PET can be a means of selecting those who are most likely to respond to chemotherapy. At present no data exists in the literature concerning the application of PET-CT in this context for hepatobiliary malignancies. However, PET imaging has been used in assessing over-expression of P-glycoprotein (associated with drug-resistant tumours) in the context of preclinical studies,12 thereby avoiding the invasive use of biopsies in determining tumour phenotype.

Metabolism and drug distribution

As discussed earlier, the choice of compound to which a radiotracer is bound to can be varied depending on the physiological or biochemical process which needs to be studied. By binding a radiotracer to an active pharmaceutical compound, the distribution of that drug and its uptake within the target tumour can be monitored. It would seem almost inevitable that these pharmacokinetic studies will evolve to the addition of CT to current PET imaging, thereby increasing the accuracy of localizing the uptake of chemotherapeutic compounds in normal versus malignant tissue. Compounds studied using PET imaging alone include fluorouracil, paclitaxel and N-cisplatin.16–18

Tumour response

Assessment of tumour response to novel chemotherapy regimens is a vital part of clinical drug trials. This allows for accurate
evaluation of the efficacy of the tested drug and can also be used to exclude patients who are not responding and may be experiencing troublesome side-effects. Conventional assessment includes CT monitoring of tumour size, spread and serum tumour markers. However, a reduction in tumour size may not be evident immediately and gives little information of drug efficacy in tumours where growth is stabilized but tumour regression has not been achieved. Some new chemotherapy compounds act in a cytostatic rather than cytotoxic fashion, further compounding the problem in using tumour size alone as a measurement of drug impact.19

By acting as a marker of tumour physiology and activity, PET-CT adds a new dimension to clinical drug trials. An example of the use of PET-CT in this setting is in the development of the tyrosine kinase receptor inhibitor, imatinib, used for the treatment of gastrointestinal stromal tumours (GISTs). In this context, PET-CT was shown to predict response to therapy, as early as 24 h after treatment.20 Early exclusion of non-viable drugs can, therefore, be achieved and so increasing the throughput of tested compounds. In addition, PET-CT can accurately stage malignancies, revealing occult metastases not visualized on conventional CT imaging, allowing a more accurate evaluation of drug response in relation to tumour burden.

**PET-CT and colorectal liver metastases assessment**

The role of PET-CT in the evaluation of colorectal hepatic metastases lies predominantly in tumour staging, specifically to detect extra-hepatic disease or occult intrahepatic metastases not evident on conventional scanning. In the context of planned liver resection, extrahepatic metastases are considered a contraindication to surgery and detecting occult disease spares these patients an unnecessary laparotomy. PET-CT fusion has been shown to consistently improve on tumour staging when compared with PET alone21,22 or if compared with parallel evaluation of independently acquired CT and PET images.23 Other potential applications of PET-CT include localization of intrahepatic tumours for ablative or resection therapy, surveillance and assessment to tumour response to intervention. At present, no studies are evident detailing the use of PET-CT as surveillance after colorectal liver metastases (CLM) resection.

**Tumour staging**

Table 1 displays current reports regarding the use of PET-CT of patients under consideration for liver resection with suspected colorectal liver metastases (CLM).24–28 The data shows that PET-CT is more accurate in the detection of extra-hepatic disease than CT alone and at least as accurate as CT in the detection of intra-hepatic disease. MRI is both accurate and sensitive in the detection of hepatic metastases with one study demonstrating it to be better than PET-CT.24 It has been previously shown that survival of PET-staged patients after hepatic resection is significantly...
improved, which is probably explained by the selection of patients without occult metastatic disease which becomes clinically evident at a later date. At present, no survival data of PET-CT-staged patients undergoing liver resection are available in the literature.

Two studies reviewed reported evidence that pre-operative chemotherapy reduces the sensitivity of PET-CT in the detection of colorectal metastases from 93 to 49%. This may be secondary to reduced metabolic activity within the metastases and so reduced SUV compared with background uptake or possibly secondary to a reduction in the size of the lesion below the resolution of PET imaging. A high rate of PET-CT false positives at the liver edge, after previous hepatic resection, has also been described with a resultant specificity of only 60%. However, other studies contradict this, with Selzner reporting a difference in sensitivity between PET-CT and conventional CT of 100% versus 50% respectively. PET-CT also demonstrates a high sensitivity in the detection of lung metastases (100%).

In the absence of long-term survival data on post-operative PET-CT-staged patients, it is difficult to fully assess the clinical impact of PET-CT. However, three of the reviewed studies reported a change in patient management in 10.7% to 21% of patients. These changes in management included avoidance of laparotomy, commencement of palliative chemotherapy or undertaking more extensive surgery than originally planned. While the data regarding PET-CT in staging for CLM is relatively sparse, one can tentatively assume that conventional imaging such as MRI or CT are at least comparable (or worse) to PET-CT in the assessment of hepatic disease, but PET-CT is more useful in the detection of extrahepatic disease.

**Intrahepatic tumour localization for surgery or ablation**

The role of intra-operative ultrasound (IOUS) during liver surgery has been shown to change the planned surgical procedure in 19% to 65% of patients. Only one study was found examining the efficacy of IOUS in patients who had undergone previous PET-CT as staging. While a direct comparison was not made between PET-CT and IOUS, the addition of IOUS was found to result in changes in management for 35% of patients. The addition of IOUS appears to be little consensus whether PET-CT should be offered routinely, or only in those patients where a clinical suspicion of occult disease is present. For staging of primary lung cancer and lymphomas, PET-CT has largely become routine staging in most centres, but more data are needed in the context of colorectal cancer metastases before any firm recommendations can be made. At present, despite some centres employing PET-CT for patients presenting with CLM, most units employ PET-CT on a selective basis. Initial staging will consist of CT and MRI, with PET-CT employed after discussion at a multidisciplinary meeting if there is a suspicion of occult disease not evident on conventional imaging or to further clarify anomalies seen but not clearly evaluated by CT or MRI.

The lack of published data regarding the cost-effectiveness of PET-CT makes a conclusive evaluation problematic. Data regarding PET in isolation suggested a cost saving of €2,671 per patient.
by avoiding inappropriate exploratory laparotomy in 6.1% of patients. In the small sample of studies examining PET-CT for CLM, a change in clinical management was evident in approximately 10% to 20% (Table 1). While this change in management covered a range of clinical procedures (an itemised breakdown was not possible from the reported data), for some patients this entailed avoiding unnecessary laparotomy. One could surmise that a similar cost saving (or possibly greater cost saving considering that PET-CT allows for greater patient throughput and reduced usage of radiotracer than PET) could be obtained with PET-CT. However, it is possible that this cost saving may not be immediately apparent. With any developing technology it is likely that patients with equivocal PET-CTs suggestive of extrahepatic recurrence may still undergo exploratory surgery to confirm or refute the findings. This pragmatic approach will doubtless improve confidence in the validity of the imaging results in the future and (combined with potential survival benefits in PET-CT-staged patients undergoing resection) may allow for a full realisation of projected cost savings.

**Inaccuracies in PET-CT**

With any imaging modality, the standard of reference used to confirm that visualized abnormalities are representative of actual pathology determines the degree of confidence with which one may interpret reports of sensitivity and specificity. The ideal is to have histological proof that the visualized lesion represents malignancy. In the context of PET-CT in staging of CLMs, all the studies reviewed used surgical findings (including IOUS and resection) as part of the standard of reference. However, for patients with a burden of disease precluding surgical exploration, obtaining histological proof may be problematic both technically and ethically. All studies reviewed relied on clinical follow-up for a proportion of the patients who did not undergo surgery. As such, it is important to appreciate that this unavoidable flaw underpins all studies assessing any new diagnostic modality. For this reason, percutaneous or intra-operative confirmation of PET-CT positive foci should be attempted if possible.

As discussed previously, lesions on the dome of the liver may be inaccurately localized by PET-CT to the right basal lung lesions, although the incidence of this appears to be very low, being detected in only 6 out of 300 patients. False positives have been reported at sites of inflammation, including suture granulomas or suture pedicles, or from retained activity within ureters, bladder or thrombus. False negatives may occur in patients who have received previous chemotherapy, cystic lesions, small volume disease and miliary peritoneal disease. Delayed PET-CT scanning may facilitate tumour detection by allowing more time for 18F-FDG to penetrate hypoxic areas within tumours and accumulate sufficiently to increase SUV above baseline detection. Careful scrutiny of the CT component of PET-CT is also essential in providing further valuable information. It has been previously shown that independent blinded review of the CT component of PET-CT images improved sensitivity and specificity from 91.4% and 63.3% to 98.6% and 100%, respectively.

**PET-CT and diagnosis of colorectal liver metastases**

PET-CT is increasingly being used in the staging and follow-up of primary colorectal cancer. As a consequence, patients are now referred for consideration for resection to hepatobiliary units with liver disease diagnosed on PET-CT. These patients represent a select group in that extra-hepatic disease will have already been excluded or been assessed for resectability (for example patients with pulmonary recurrences). In addition, data from studies examining evidence of PET-CT efficacy only in the exclusion of local or extra-hepatic recurrence, adds further information regarding the ability of PET-CT to detect such extra-hepatic sites of recurrence as compared with conventional imaging. For these reasons, an overview of the use of PET-CT in primary colorectal cancer is of interest and offers important insights to hepatobiliary surgery.

The papers reviewed were restricted to those evaluating the diagnostic application of PET-CT in the staging or surveillance of primary colorectal cancer. Manuscripts detailing the use of PET-CT for radiotherapy planning or virtual colonography were not examined, as this was not relevant to hepatobiliary practice. The data are summarized in Table 2. For the most part, the data show increased sensitivity and specificity of PET-CT in detecting lymph node disease, hepatic, extra-abdominal and extrahepatic recurrence/metastases when compared with PET and/or CT. These observations further support the use of PET-CT in staging CLMs particularly with regards to the exclusion of extrahepatic disease prior to resection.

**PET-CT and hepatocellular carcinoma**

Only 30% to 50% of primary hepatocellular carcinomas (HCC) demonstrate 18F-FDG uptake above background levels. High levels of glucose-6-phosphatase are found in normal liver and HCCs leading to dephosphorylation of 18F-FDG, which subsequently no longer accumulates in cells and redistributes back into the circulation. For this reason, PET-CT has limited application in the evaluation of intra-hepatic HCCs. More recently an alternative tracer (11C- acetate) has been used in conjunction with 18F-FDG which improves visualization of these lesions. The degree of HCC differentiation determines its relative avidity for one of the two probe molecules. Well-differentiated HCCs demonstrate negative uptake on 18F-FDG and positive uptake with 11C-acetate, while poorly differentiated HCCs display the reverse characteristics. Moderately differentiated HCCs will show a mixed affinity in various parts of the tumour between the two tracer molecules. While this combination of tracers (dual tracer PET-CT) may offer better imaging of HCCs, its application has not yet been reported.
The short half-life of $^{11}$C-acetate limits its applicability only to centres with an on-site cyclotron. An alternative probe is the compound $^{18}$F-Fluorocholine. Choline is one of the components of phosphatidylcholine, a component of the phospholipids found in all cell membranes. In cancers, rapid cell duplication results in active uptake of choline. $^{18}$F-Fluorocholine has a longer half-life than $^{11}$C-acetate, which allows for its use in a greater number of centres and also enables delayed imaging, improving the quality of images obtained. HCCs are significant accumulators of choline as a result of rapid cell turnover. At present, only small numbers of patients have been assessed using $^{18}$F-Fluorocholine PET-CT in comparison to standard $^{18}$F-FDG PET-CT. The results suggest improved accuracy of $^{18}$F-Fluorocholine PET-CT in detecting both intrahepatic and recurrent extrahepatic HCCs in 12 patients assessed using these techniques. No large-scale study comparing $^{18}$F-Fluorocholine PET-CT with MRI or CT imaging is presently available in the literature.

A single-centre experience of dual tracer $^{11}$C-acetate and $^{18}$F-FDG PET-CT has been reported in the evaluation of metastatic HCC. Dual tracer imaging was found to be approximately 70% sensitive with a change in management initiated in 19% of studied patients as a result of the imaging acquired. Other studies reporting the use of $^{18}$F-FDG PET-CT are largely limited to case reports detailing its use in detecting omental HCC recurrence or portal vein tumour thrombus. $^{18}$F-FDG PET-CT has been reported as being more accurate than CT alone in the detection of recurrent intrahepatic HCC after transcatheter arterial embolization (TACE) or radiofrequency ablation (90.9% accuracy vs. 45.4% respectively) in a series of 13 patients. However, for the most part, current PET-CT technology limits its application in the assessment of hepatocellular carcinoma.

**PET-CT and gall-bladder cancer and cholangiocarcinoma**

Only three studies were found detailing PET-CT in the staging and surveillance of cholangiocarcinomas and gallbladder cancers, the data are summarised in Table 3. There are not enough data to make a meaningful comparison between PET-CT and MRI in the imaging of cholangiocarcinomas, but most studies reported PET-CT to be better than conventional CT scanning in the assessment of primary lesions, and in particular, in the detection of distant unexpected metastatic spread including regional lymph nodes and more distant sites of metastases. Of note, is a marked reduction in sensitivity and specificity of PET-CT in the characterization of extrahepatic versus intrahepatic cholangiocarcinomas. PET-CT has also been shown to be of some value in differentiating between benign and malignant hilar strictures. These encouraging preliminary reports need consolidation from other centres before firm conclusions can be drawn.
Table 3 Table summarizing data regarding positron emission tomography-computed tomography (PET-CT) in the characterization of other hepatobiliary malignancies excluding neuroendocrine tumours

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study type</th>
<th>Cancer studied</th>
<th>Number of patients</th>
<th>Change in clinical management</th>
<th>Context of scan</th>
<th>Assessment of primary lesion</th>
<th>Assessment of lymph node status</th>
<th>Assessment of other metastatic spread</th>
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<tr>
<td>Quon et al.</td>
<td>2008</td>
<td>Prosp</td>
<td>Panc</td>
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<td>FLT tracer resulted in detection in 40% of patients vs. 100% using 18F-FDG PET-CT</td>
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<td>Kim et al.</td>
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<td>Cholangio</td>
<td>123</td>
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<td>S &amp; D</td>
<td>No difference between PET-CT, MRCP or CT</td>
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<td>Panc</td>
<td>46</td>
<td>-</td>
<td>D</td>
<td>PET-CT Abdominal USS ERCP Endoscopic USS Comparison with other imaging in detection of malignancy</td>
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<td>Retro</td>
<td>Cholangio</td>
<td>24</td>
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<td>SR</td>
<td>91.2% accuracy 88.2% accuracy 85.3% accuracy 83.8% accuracy</td>
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<td>Prosp</td>
<td>Panc</td>
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<td>Reinhardt et al.</td>
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<td>-</td>
<td>Cholangio</td>
<td>22</td>
<td>-</td>
<td>SUV of 6.8 vs. 3.3 between malignant and benign hilar strictures (P = 0.003)</td>
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<td>Tann et al.</td>
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<td>Retro</td>
<td>Panc</td>
<td>30</td>
<td>-</td>
<td>86 90 71 91 91</td>
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</table>

MRCP, magnetic resonance cholangiopancreatography; USS, ultrasound scan; SR, suspected recurrence; ERCP, endoscopic retrograde cholangiopancreatography; S, preoperative staging; D, Diagnosis; Pancyst, pancreatic cystic lesions; Sens, sensitivity; Panc, pancreatic adenocarcinoma; Spec, specificity; Cholangio, cholangiocarcinoma; GB, gallbladder cancer.
PET-CT in and pancreatic cancer

Pancreatic adenocarcinoma

PET imaging alone has a reported sensitivity of 82% to 100% and a specificity of 67% to 100% in the diagnosis of pancreatic adenocarcinoma.24-26 Hypoxia in CLMs has been postulated in being a cause for poor 18F-FDG uptake.28 Pancreatic adenocarcinomas, in particular, show evidence of hypoxic tumour cores,27 which may result in poor uptake of 18F-FDG and render their characterization by PET-CT sub-optimal. In addition, background inflammatory changes within the pancreas (such as chronic pancreatitis) may also result in increased 18F-FDG uptake, rendering the detection of small pancreatic lesions problematic.28 18F-fluorothymidine (FLT) has also been proposed as a new radiotracer which assesses cells undergoing active proliferation. There is one report of 18FFLT used in a series of five patients with pancreatic adenocarcinoma compared with standard 18F-FDG PET-CT.31 Despite the small numbers of patients, the results do not suggest any advantage over 18F-FDG (Table 1).

The paucity of relevant data suggests that PET-CT is not currently routinely used in the diagnosis or surveillance of pancreatic adenocarcinoma. Prospective data of PET-CT in detecting pancreatic lesions have shown it to be no worse than traditional investigative modalities such as endoscopic retrograde cholangiopancreatography (ERCP), endoscopic or abdominal US.23 Interestingly, no comparison with conventional CT was made in the study (Table 3), but other prospective data do not suggest a significant advantage of PET-CT compared with multi-row detector CT in the diagnosis, staging or surveillance of pancreatic tumours.86 A prospective study by Heinrich et al. reported PET-CT to have broadly equivalent sensitivities to conventional CT in the diagnosis of the primary lesion but improved specificity (Table 3). For distant metastases, PET-CT was more sensitive than conventional CT and changed management plans for 16% of people (deemed resectable after conventional staging), which equated to a cost saving of $62,912 per patient.27 The cost-effectiveness analysis provided by the authors, has been subsequently criticized as confusing and the point has been raised that a negative PET-CT does not rule out cancer with any degree of certainty, although a positive PET-CT is of value in the assessment of these lesions.79

The remaining literature describing PET-CT in the evaluation of pancreatic cancer consists of case reports detailing isolated experiences of PET-CT in detecting distant metastatic spread69 or tumour thrombus61 and proposing the use of PET-CT in evaluation treatment response of pancreatic tumours after radiotherapy.62 These manuscripts are mentioned for completeness, but are not included in Table 3.

Cystic lesions of the pancreas

Cystic lesions of the pancreas represent a difficult problem to the hepatobiliary surgeon in excluding premalignant or malignant lesions from benign. A wide range of different investigations are generally required including cross-sectional imaging, laparoscopic/endoScope ultrasonound and cytological/biochemical analysis of cyst fluid to obtain a diagnosis. The decision to resect such lesions may, on occasion, be made on size alone if no clear-cut classification can be made pre-operatively.83 The additional physiological information provided by PET-CT could prove a valuable addition to the multi-modality assessment currently employed. In this context, PET-CT has been found to more sensitive than conventional CT, although specificities were not significantly different.84 PET in isolation has also been described, in the form of a case report of a single patient, to detect a focus of malignancy in intraductal papillary mucinous tumours (IPMTs), but no other data are present to support the use of PET-CT for pancreatic cystic lesions.85

Neuroendocrine tumours

Neuroendocrine tumours are a broad group of tumours derived from endocrine cells, with the capacity to produce a variety of biogenic amines and polypeptides. The classification of neuroendocrine tumours is dependent upon the size of the tumour and proliferation rate.86 Three classes of neuroendocrine tumours are described which are Type 1a (well-differentiated; Ki67 <2%), Type 1b (well-differentiated; Ki67 2 to 10%) and Type II (poorly differentiated).86 In spite of this, the anatomical origin of neuroendocrine tumours determines the nature and type of resection and neuroendocrine tumours (NET) represent a consistent (albeit small) component of the referral load for the hepatobiliary surgeon. An overview of PET-CT imaging in the investigation of all NETs will be presented, where possible data specifically related to NETs of hepatobiliary origin will be included.

An important feature of NETs is that because of their functional nature, they may present with marked symptoms early, before the primary tumour is large enough to be found with conventional imaging, for this reason functional imaging may be the sole means of accurate diagnosis and localizing a small lesion. Four different types of radiotracers have been employed in the characterization of NETs. The most common is 18F-FDG, with the other radiotracers being developed to target specific functional properties of NETs. Well-differentiated NETs are indolent tumours with a low metabolic turnover and so may not be imaged clearly on standard 18F-FDG radiotracer PET-CTs. In contrast, fast-growing and poorly differentiated tumours may lose their functional ability and thus be less ‘visible’ with the novel radiotracer techniques detailed below. Hence, a combination of glucose metabolism probes and functional NET probes may compliment each other in detecting NETs and providing information regarding the degree of tumour differentiation.

Some NETs have the ability to take up and decarboxylate amine precursors, such as dihydroxyphenylalanine (DOPA) and hydroxytryptophane, leading to their alternative eponym of amine precursor uptake and decarboxylation (APUD) tumours.87 Radiolabelled amine precursors can thus be employed such
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study type</th>
<th>Radiotracer used</th>
<th>Target tumour</th>
<th>Number of patients</th>
<th>Context of scan</th>
<th>Assessment of primary lesion (s)</th>
<th>Assessment of other metastatic spread</th>
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<tr>
<td></td>
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<td>PET-CT</td>
<td>SRS</td>
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<tr>
<td>Kayani et al.</td>
<td>2008</td>
<td>Prosp</td>
<td>18-F-FDG, 68Ga-DOTATE</td>
<td>GI, Pol &amp; unknown</td>
<td>38</td>
<td>S and SR</td>
<td>66 –</td>
<td>Predominant uptake of 18-F-FDG or 68Ga-DOTATE showed significant correlation with tumour stage (P &lt; 0.001)</td>
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<tr>
<td>Koopman et al.</td>
<td>2008</td>
<td>–</td>
<td>DOPA, 11C-HT</td>
<td>PIT</td>
<td>23</td>
<td>S</td>
<td>80 –</td>
<td>77 –</td>
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<td>Wieder et al.</td>
<td>2007</td>
<td>Prosp</td>
<td>Gluc-Lys</td>
<td>GI &amp; Pol</td>
<td>10</td>
<td>S</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Wieder et al.</td>
<td>2007</td>
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<td>DOPA</td>
<td>GI</td>
<td>84</td>
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<td>Seemann et al.</td>
<td>2007</td>
<td>Prosp</td>
<td>Gluc-Lys</td>
<td>GI</td>
<td>31</td>
<td>S &amp; SR</td>
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<td>Seemann et al.</td>
<td>2006</td>
<td>Prosp</td>
<td>Gluc-Lys</td>
<td>GI</td>
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<td>S</td>
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</table>

SR, suspected recurrence; GI, gastrointestinal; S, preoperative staging; Pol, pulmonary; D, diagnosis; Gluc-Lys, Gluc-Lys-[^18F]FP-TOCA; somatostatin receptor analogue; Sens, sensitivity; DR, detection rate; Spec, specificity; HT, 11C-hydroxytryptophane; DOPA, 18-F-dihydroxyphenylalanine; SRS, somatostatin receptor scintigraphy; PIT, pancreatic islet cell tumour. 

*SRS and CT fusion. 
^Somatostatin receptor analogue.
as $^{11}$C-hydroxytryptophane (HT), $^{18}$F-dihydroxyphenylalanine (DOPA) or $^{18}$F-fluorodopamine. NETs over-express a variety of peptide receptors including somatostatin receptors, which has been previously exploited in somatostatin receptor scintigraphy. A more recent development is $^{68}$Gadolinium-labelled somatostatin analogues which can be detected with PET cameras, leading to higher resolution of small NETs. Finally, $^{11}$C-hydroxyephedrine or $^{13}$C-metomidate can also be employed, which are concentrated in adrenal tissues in particular. Both radiotracers are accumulated as a consequence of the synthesis of cortisol and aldosterone in the adrenal cortex.

It is not possible to compare radiotracer efficacy used in PET-CTs for NETs, because of the wide range of different compounds currently in usage. Overall, the data show that PET-CT is consistently more accurate and sensitive than CT alone, MRI and somatostatin scintigraphy (Table 4). In the assessment of liver lesions, PET-CT would not appear to be significantly better than MRI scanning, but is more accurate in the detection of osseous disease or lymph node disease. MRI and PET fusion was found by one study to be better than CT, PET-CT or MRI alone in the detection of liver, lymph node and osseous disease with detection rates of 100%, 97.3% and 100%, respectively. It is likely that a combination of PET-CT radiotracers, used in conjunction with conventional imaging, may offer the best yield of clinical information. Dual tracer PET-CT has been shown to offer information on tumour staging and to improve overall sensitivity from 66% and 82% (used independently) to 92%.

### Conclusion

Since its introduction, PET-CT has been employed in the characterization of a wide range of malignancies. The indications and relative indications for PET-CT are summarized in Fig. 3. It is probable that some of these indications may change with time. PET-CT is now an accepted part of staging and diagnosis for primary colorectal cancer and CLMs. However, it still not clear if PET-CT should be used routinely for such patients or only after discussion at multidisciplinary team (MDT). There is growing evidence of the efficacy of PET-CT in the evaluation of pancreatic masses and neuroendocrine tumours, but at present more clinical data are required before PET-CT becomes a routine investigation in the assessment of these malignancies. The data for PET-CT in the context of cholangiocarcinoma and in particular, in diagnosis and staging of gallbladder cancer are insufficient at present to allow for a conclusive recommendation to be made. Finally, PET-CT would appear to have the least impact in the management for hepatocellular cancer, although, with the development of dual-tracer PET-CT, this may change in the future.

### Conflicts of interest

None declared.

### References


