The role of $^{18}$FDG PET/CT in the management of colorectal liver metastases

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Abstract

Introduction: Surgical resection remains the only potentially curative treatment for colorectal liver metastases (CLM). However, involvement of both the hepatic lobes or extrahepatic disease (EHD) can be a contra-indication for resection. The aim of the present study was to examine the addition of combined positron emission and computed tomography (PET/CT) to CLM staging to assess the effects upon staging and management.

Methods: All CLM patients referred to a single centre between January 2005 and January 2009 were prospectively included. All underwent routine staging (clinical examination and computed tomography), followed by a whole body $^{18}$fluoro-deoxy-glucose ($^{18}$FDG)-PET/CT scan and Fong clinical risk score calculation.

Results: Sixty-four patients were included [63% male with a median age of 63 years (age range 32–79 years)]. The addition of PET/CT led to disease upstaging in 20 patients (31%) and downstaging in two patients (3%). EHD was found in 24% of low-risk patients (Fong score 0–2) as compared with 44% of high-risk patients (Fong score 3–5) ($P = 0.133$). There was a trend towards a greater influence upon management in patients with a low score (44% vs. 17%; $P = 0.080$).

Conclusion: The addition of PET/CT led to management changes in over one-third of patients but there was no correlation between alterations in staging or management and the Fong clinical risk score; suggesting that PET/CT should be utilized, where available, in the pre-operative staging of CLM patients.

Keywords
colorectal metastases, liver resection, liver

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Introduction

Over 37,000 diagnoses of colorectal cancer (CRC) are made per annum in the UK, up to 9000 of which will have liver metastases at the time of diagnosis, and approximately 50% of which will develop spread to the liver during the course of disease; where they will be responsible for up to two-thirds of all CRC deaths. The management of colorectal liver metastases (CLM) continues to evolve but surgical resection remains the only potentially curative treatment and the current approach is that resection is indicated if the metastases are resectable and sufficient residual liver will remain post-operatively to prevent hepatic failure. Current contra-indications to resection include a non-treatable primary tumour or widespread nodal, locoregional or metastatic (pulmonary, bony and peritoneal) disease; although, certain patients with resectable or ablative extrahepatic disease (EHD) remain suitable for resection.

Overall, survival rates after resection for CLM are 26–60% at 5 years, 17–26% at 10 years and 26% for those with EHD; whereas, post-operative mortality is 1.5–2.8%. Recurrence within the liver is the commonest cause of treatment failure; however, second or third resections can be performed for recurrent metastases with similar 5-year survival rates to first resection (34% and 32% respectively) and an acceptable post-operative morbidity rate.
However, even within selected subgroups of patients with resectable disease, there is wide variability in recurrence rates and survival after resection. Independent predictors of poor survival after resection include multiple hepatic metastases, a poorly-differentiated or node positive primary tumour, EHD, tumour diameter ≥5 cm, significantly raised carcinoembryonic antigen levels (CEA), positive resection margins and a short disease-free interval from development of primary to development of metastases (less than 12 months). Reliable, prognostically accurate and widely-applicable molecular markers for CLM are yet to be identified, and such disease-related clinical variables are often utilized to risk-stratify patients. In 1999 Fong et al. assessed 1001 consecutive CLM patients to become the first group to synthesize a pre-operative clinical risk score. The Fong score incorporated node status, number and size of tumour, disease-free interval and CEA level (see Table 1) in a fashion that was found to be highly predictive of outcome: low scores (two or less out of five) were associated with a favourable outcome, whereas high scores (five out of five) were not associated with a long-term prognosis (see Fig. 1).

The accuracy of pre-operative staging is pivotal for the correct implementation of such scoring systems and a number of modalities are routinely utilized to image the liver, including ultrasound (US), contrast-enhanced multi-detector computed tomography (CEMDCT) and magnetic resonance imaging (MRI). However, many of these techniques remain limited as the tumour burden is often underestimated, particularly in extra-hepatic disease. Combined positron emission and computerized tomography (PET/CT), utilizing 18-fluoro-deoxy glucose (18FDG) produces a fusion image combining conventional cross-sectional, anatomical imaging of CT with the biological, functional imaging of PET. It can be utilized to identify and stage primary colorectal tumours as well as metastases and has also been used to great effect in the staging of anal squamous cell, pancreatic and lung cancers.

The present study examined the pre-treatment staging of CLM by PET/CT to investigate whether it could alter the staging of local or distant disease and management. Further, we aimed to compare the Fong clinical risk score with PET/CT yield in an attempt to stratify the use of PET/CT in patients with CLM.

### Table 1 Fong score criteria for determination of prognosis in patients with colorectal liver metastasis (CLM). The patient scores one point for each criteria they meet (adapted from Fong et al.11)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymph node + ve primary tumour</td>
<td>1</td>
</tr>
<tr>
<td>Disease-free interval &lt; 12 months</td>
<td>1</td>
</tr>
<tr>
<td>≥1 Tumour</td>
<td>1</td>
</tr>
<tr>
<td>Tumour size &gt; 5 cm</td>
<td>1</td>
</tr>
<tr>
<td>CEA level &gt; 200 ng/ml</td>
<td>1</td>
</tr>
</tbody>
</table>

CEA, carcinoembryonic antigen.

### Methods

#### Patients and staging

All patients referred to a single centre for potential resection of CLM, between January 2005 and January 2009, were prospectively included in the present study. All had previously undergone R0 (complete histological clearance) resection of a primary colorectal tumour and all patients underwent routine staging, consisting of clinical examination and a CEMDCT scan of the thorax, abdomen and pelvis. All patients also underwent a whole body 18FDG-PET/CT scan performed within 2 weeks of CEMDCT at the same institution, as part of their standard pathway of care (therefore, no ethical approval was sought for the study).

A clinical risk score was calculated for each patient (range 0–5), as per the Fong criteria (see Table 1 and Fig. 1): a clearly-defined and widely-applicable score of clinical criteria for the selection of patients likely to benefit from resection of CLM. The patients were divided into low risk (Fong score 0–2; five-year survival 40% or higher) and high risk for recurrence (Fong score 3–5; five-year survival 20% or less), as per the original scoring system.

All patients were reviewed in a specialist hepatobiliary, multi-disciplinary team (MDT) meeting, consisting of hepatobiliary surgeons, oncologists, pathologists and radiologists with an interest in radiofrequency ablation (RFA). The MDT was initially blinded to the results of the PET/CT scans, which were reported by a dual-trained nuclear medicine and radiology physician with over 5 years experience of reviewing PET/CTs, and who in turn was blinded to the results of the standard imaging. A PET/CT lesion was identified as being ‘positive’ according to the considered opinion of the reporting physician. An initial management decision was made based upon standard imaging and the results of the PET/CT scan were subsequently revealed and a new management plan created. The results of the PET/CT scan results were then correlated with the Fong clinical risk score.

#### PET/CT protocol

One hour before the examination, 370MBq of 18FDG was injected intravenously. Utilizing a dedicated combined GE Discovery LS PET/CT unit (GE Advance PET scanner and the GE Light-speed CT; General Electric Company, Fairfield, CT, USA), whole-body examinations were performed with the patient supine and arms held above the head. CT was performed using four 3.75-mm detectors, a pitch of 1.5 and a 5-mm collimation. The CT exposure factors for all examinations were 140 kVp and 80 mA in 0.8 s. Maintaining the patient position, a whole body PET emission scan was performed, covering an area identical to that of a CT (5–6 bed positions). All acquisitions were carried out in a 2-dimensional (2D) mode and consisted of emission scans of 5 min per bed position. PET images were reconstructed using CT for attenuation correction by employing CT maps. Transaxial emission images of 4.3 × 4.3 × 4.25 mm³ (in plane matrix size 128 × 128) were reconstructed using ordered subsets expectation maximization (OSEM).
with two iterations and 28 subsets. The axial field of view was 148.75 mm, resulting in 35 slices per bed position.

**Statistical analysis**

Statistical analysis was performed using an SPSS (Statistical Package for the Social Sciences Inc., Chicago, IL, USA) software package. Two-tailed \( P \)-values less than 0.05 were considered statistically significant.

**Results**

**Demographics**

Sixty-four consecutive patients with colorectal liver metastases, all of which had undergone PET/CT as part of their standard pathway of care, were included in the present study. Forty (63%) were male and the median age was 63 years (age range 32–79 years). None of the patients underwent neoadjuvant chemotherapy.

**Effect of PET/CT inclusion in the staging protocol**

Inclusion of PET/CT in the staging protocol resulted in additional information in 28 patients (43%) and a change of management in 22 patients (34%).

Management changes occurred secondary to disease upstaging in 20 patients (31%) and downstaging in two patients (3%).

Disease upstaging occurred as a result of the discovery of peritoneal disease in six patients, retroperitoneal lymph nodes in four patients, mediastinal lymph nodes in two patients, porta hepatis nodes in one patient and a previously undiagnosed thyroid cancer with bone metastases in a further patient. Thirteen out of 20 lesions identified were new, whereas seven had been labelled as indeterminate or suspicious on CT alone (two patients with peritoneal disease, two with retroperitoneal lymphadenopathy, two with lung lesions and one with porta hepatis nodes). The patient with thyroid cancer underwent resection to remove the thyroid lesion; however, primary treatment for CLM in upstaged patients was changed from surgical resection to chemotherapy.

The two patients downstaged were reported to have lung metastases on CEMDCT; however, the lung lesions were not FDG avid and were therefore thought to represent chronic airways disease after PET/CT. Both patients were subsequently deemed fit for surgery after pre-operative optimization.

**Comparison with Fong clinical risk scores**

Of the 64 patients, 46 (72%) had Fong scores of 0–2 (low-risk of recurrence) and 18 (28%) had scores of 3–5 (high-risk of recurrence).

Eleven out of 46 low-risk patients were found to have EHD on PET/CT, as compared with eight out of 18 high-risk patients (Fisher’s exact test: \( P = 0.133 \)). However, although not significant, there was a trend towards a greater influence upon management in those patients with a low clinical risk score (0–2): 20 out of 46 low-risk patients underwent management alterations after PET/CT, as compared with only three out of 18 high-risk patients with a clinical risk score of 3–5 (Fisher’s exact test: \( P = 0.080 \)).

**Discussion**

The results of the present study demonstrate that the use of PET/CT in CLM patients is associated with alterations in patient management in approximately one-third of patients (34%) (par-
ticularly owing to disease upstaging) but that there was no correlation between alterations in staging or management and the Fong clinical risk score.

Biological and multi-modality imaging, in the form of PET and PET/CT, are now being increasingly utilized within the UK. PET/CT works via the preferential accumulation and metabolic trapping of a radiolabelled glucose analogue, 2-[18 F] fluoro-2-deoxy-D-glucose (FDG), within malignant cells. The functional nature of the image rendered, which relies upon a metabolic evaluation of glucose uptake, rather than size or morphological criteria alone, may allow the evaluation of smaller tumours at an earlier point in their natural history, and a true integrated PET/CT system also allows good anatomical definition by circumventing the lack of an anatomical reference frame found with isolated PET.

A meta-analysis performed by Kinkel et al. in 2002 found that FDG-PET was the most sensitive method for the detection of liver metastases from multiple gastrointestinal origins, with a mean weighted sensitivity of 90–92%, a result confirmed by Arulampalam et al. in two separate studies: one investigating 42 patients with suspected recurrent CRC to discover that FDG-PET was more accurate than CT (sensitivity 100% vs. 45%; specificity 100% for both) and one in 28 patients with confirmed CLM to demonstrate a sensitivity and specificity of FDG-PET of 100% and 91%, respectively, as compared with 47% and 91% for CT. More recent meta-analyses confirm these initial results. A meta-analysis of 25 articles published between 2000 and 2008 demonstrated that sensitivity and specificity, on a per-patient basis, for ultrasound, CT, MRI and FDG-PET in the detection of CLM were 63.0% and 97.6%, 74.8% and 95.6%, 81.1% and 97.2, and 93.8% and 98.7%, respectively; whereas, on a per lesion basis sensitivity was 86.3%, 82.6%, 86.3% and 86.0%, respectively. Further, Wiering et al. found that FDG-PET had a pooled sensitivity and specificity of 88.0% and 96.1%, respectively, for hepatic disease, and 91.5% and 95.4% for EHD, results that were significantly higher than CT (82.7% and 84.1% for hepatic; 60.9% and 91.1% for EHD).

Integrated PET/CT has also been shown to be superior to PET alone in the assessment of primary colorectal tumours, as well as recurrent and metastatic disease, and results to date suggest that it may also be superior to many imaging modalities in the assessment of liver metastases. Cohade et al. performed a retrospective review of 45 CRC patients to show that more definitely normal and definitely abnormal lesions were identified with PET/CT than with PET alone. The accuracy of staging and restaging also improved from 78% to 89%.

Grassetto et al. similarly assessed a mixed cohort of patients with solitary liver metastases (18 CRC, 15 non-small cell lung cancer, six breast carcinoma and four ovarian cancer) to demonstrate that PET/CT restaged disease and changed therapy in 28% of patients. Chua et al. compared CEMDCT and FDG-PET/CT in 131 patients with liver metastases (75 CRC and 56 other tumours) to show that PET/CT yielded a sensitivity and specificity of 94% and 75%, compared with 91% and 25%, respectively, for CEMDCT. Improvements in staging accuracy were associated with alterations in patient management in 25% of patients.

Discovery of such EHD has been shown to be crucial in preventing unnecessary intervention. Wiering et al. prospectively compared 100 CLM patients staged via conventional techniques, with 103 patients staged with an additional FDG-PET to demonstrate a reduction in the number of negative laparotomies by more accurate prediction of EHD. Similarly, Ruers et al. randomized 150 CLM patients selected for surgical resection by CT imaging alone (n = 75) or CT plus FDG-PET (n = 75) to demonstrate a significantly decreased number of futile laparotomies (45% vs. 28%; P = 0.042).

In those deemed unsuitable for operative intervention, systemic chemotherapy regimes can be used in a subset (12.5%) of patients to reduce tumour load and potentially allow certain patients to subsequently undergo resection. The use of FDG-PET in such circumstances may have additive effects in the monitoring of tumour metabolism and response: Vriens et al. examined the effects upon CLM functional tumour metabolism assessed by FDG-PET, prior to and following three chemotherapy cycles in 23 CLM patients to find that glucose metabolic rates decreased significantly during treatment (P < 0.001).

Currently, PET/CT is not readily available within the UK: the technology remains relatively novel, as well as being expensive and constantly evolving, and there is a shortage of PET/CT scanners, as well as trained and experienced staff available to operate them. Further, new technologies are being constantly discovered and investigated, with some groups even looking at computer-automated discovery of liver lesions.

After the development of the Fong score, five large predictive models have been published with considerable overlap of key independent predictors of long-term outcome. Utilization of such prognostic scores yields stark differences between patients in good- and poor-risk categories, with 5-year survival rates ranging from 60% to <15%, respectively. However, there remains a need for a universally-adopted predictive model, which may be used to pre-operatively improve selection for surgery, and post-operatively risk-stratify patients who may benefit from intensive surveillance and adjuvant therapies.

**Conclusion**

This article presents 64 prospectively-studied CLM patients to demonstrate that the addition of PET/CT to staging provided additional information, in particular the discovery of EHD that led to management changes in 34% of patients. These data suggest that PET/CT should be used where available in the pre-operative staging of these patients.

The influence on management provided by the addition of PET/CT was undoubtedly greater in the lower risk group (44%) than the high risk group (14%) but this failed to reach statistical significance. Based on this series, the Fong clinical risk score...
should not be used to rationalize the use of PET/CT in those patients being investigated for potential resection of CLM.

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Conflicts of interest
None declared.

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