Outcome of indeterminate liver lesions on computed tomography in patients with colorectal cancer

E Mohamed, A Adiamah, WK Dunn, Y Higashi, IC Cameron, D Gomez

Nottingham University Hospitals NHS Trust, UK

ABSTRACT

INTRODUCTION The aim of this study was to determinate the outcome of indeterminate liver lesions on computed tomography (CT) in patients with a background history of colorectal cancer (CRC) and to identify clinicopathological variables associated with malignancy in these lesions. A secondary aim was to devise a management algorithm for such patients.

METHODS Patients referred to our institution with indeterminate liver lesions on CT with a background history of CRC between January 2012 and December 2014 were included in the study. Clinicopathological factors, surveillance period and histological findings were analysed.

RESULTS Fifty-six patients with indeterminate liver lesions were identified. Fifty-three (94.6%) of these required further imaging (magnetic resonance imaging [MRI; $n=50$] and positron emission tomography combined with CT [$n=3$]). For the patients who had MRI, the underlying diagnosis was benign in 19 and colorectal liver metastasis (CRLM) in 8 while 23 patients had an indeterminate lesion. In cases that remained indeterminate following MRI, liver resection was performed in 2 patients for a high suspicion of CRLM while the 21 remaining patients underwent interval surveillance (median: 9 months, range: 3–52 months). Of these 21 patients, 14 had benign lesions while CRLM was noted in 6 patients and an incidental hepatocellular carcinoma in a single patient. Age ≥ 65 years was the only statistically significant clinicopathological factor in predicting an underlying malignancy in patients with indeterminate liver lesions on CT.

CONCLUSIONS Over a third of the patients diagnosed with indeterminate liver lesions on CT subsequently showed evidence of CRLM. These indeterminate lesions are more likely to be malignant in patients aged ≥ 65 years.

KEYWORDS

Colorectal liver metastases – Chemotherapy – Liver resection

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CORRESPONDENCE TO

Dhanwant Gomez, E: dhanny.gomez@nuh.nhs.uk

Colorectal cancer (CRC) is a leading cause of cancer related death in the UK and worldwide.¹ Significant advances have been made that have increased the resection rates for colorectal liver metastases (CRLM). These include the establishment of specialised multidisciplinary team (MDT) meetings for CRLM patients,^{2,3} improvements in radiological imaging technologies⁴ and downstaging chemotherapy in addition to the use of biological agents.⁵

Computed tomography (CT) is increasingly being employed as an initial screening tool in the assessment of patients with CRC because of its wide availability, and its ability to show both the local burden of the disease in addition to the presence of distant metastasis. However, CT has shown limitations in characterising small hepatic lesions (<1cm) that do not fit the typical radiological criteria for metastasis. The incidence of detecting these indeterminate liver lesions ranges from 12.7% to 25.5%.^{6,7}

The diagnostic challenge with this clinical entity is further fostered by the common prevalence of small hepatic

tumours such as benign haemangiomas and areas of focal nodular hyperplasia in the general population that can make the distinction between benign and malignant lesions difficult.⁶ Previous studies have shown that magnetic resonance imaging (MRI) of the liver is superior to CT in the characterisation of these hepatic lesions.^{8–10}

Recent literature has reported an association between raised systemic inflammatory markers (eg C-reactive protein [CRP], neutrophil-to-lymphocyte ratio [NLR] and/or platelet-to-lymphocyte ratio [PLR]) and poorer survival in patients with CRLM.^{11–15} This suggests the presence of a ‘tumorigenic’ inflammatory response that may underpin an aggressive tumour biology and could therefore assist in predicting liver metastases in cases of indeterminate liver lesions.

Currently, there is no consensus view on the management of indeterminate liver lesions in patients with a background of CRC. The aim of this study was to assess the fate of indeterminate liver lesions on CT and to identify

clinicopathological variables associated with the presence of an underlying malignancy. A secondary aim was to develop a management algorithm for such patients.

Methods

Patients with a background of CRC referred from both local and regional hospitals to the hepatobiliary and pancreatic unit at Queen's Medical Centre in Nottingham between January 2012 and December 2014 were identified from a specialised CRLM MDT registry. All patients were discussed by a MDT that consisted of hepatobiliary surgeons, oncologists, radiologists, pathologists and cancer nurse specialists.

Patients who were diagnosed with indeterminate liver lesions following review of CT in the MDT meeting were included in the analysis. These patients had lesions that were labelled as 'indeterminate', 'difficult/too small to characterise' or 'further imaging advised' on their official CT report. In addition, all imaging was reviewed independently by one of two experienced liver radiologists prior to the weekly meeting. Patients with liver lesions that were definitively characterised with confidence as benign or malignant or those who had a previous history of another primary cancer with an ability to metastasise to the liver were excluded from the study. All subsequent surveillance follow-up imaging for indeterminate liver lesions was reviewed again by a radiologist with an interest in hepatobiliary radiology as part of a MDT meeting.

This study was approved by the local clinical audit leads at Nottingham University Hospitals NHS Trust. Given the retrospective nature of the study, the need for individual patient consent was waived and all local ethical guidelines for retrospective studies in the trust were adhered to. Clinical data included preoperative patient demographics, serum laboratory test results, type of resection and histopathological results. The white cell and differential counts as well as CRP and carcinoembryonic antigen (CEA) levels were obtained at the time of referral to the MDT. The NLR was determined from the differential count by dividing the absolute neutrophil count by the absolute lymphocyte count. A NLR of ≥ 5 was considered raised.¹¹ The PLR was obtained by dividing the absolute platelet count by the absolute lymphocyte count, with a PLR of ≥ 150 being considered raised.¹² CRP $>10\text{mg/l}$ and CEA $>5\mu\text{g/l}$ were also considered raised.¹⁴

Imaging protocols

Radiological imaging included CT of the thorax, abdomen and pelvis. Supplementary imaging with MRI of the liver and (in some instances) positron emission tomography (PET) combined with CT was also performed after review of CT. Contrast enhanced imaging of the thorax, abdomen and pelvis was obtained using multirow detector CT scanners with collimation of $2 \times 0.625\text{mm}$. The imaging was performed from just above the superior aspect of the lungs to below the ischial tuberosities. Contiguous axial images (1.5–8mm thick) were reconstructed from the data. Oral and 100ml intravenous contrast was administered at an average rate of 3ml per second (Niopam® 300; Bracco, High Wycombe, UK).

MRI was performed at 1.5T using liver specific contrast: either gadoxetic acid (Primovist®; Bayer, Reading, UK) or gadobenetic acid (MultiHance®; Bracco). Standard protocols were used; these varied slightly depending on the machine and contrast but included precontrast T2 and T1 opposed-phase, diffusion weighted, dynamic contrast enhanced spoiled gradient echo T1, and delayed liver specific phase spoiled gradient echo T1 sequences.

PET-CT was performed with a Discovery™ 710 scanner (GE Healthcare, Chalfont St Giles, UK). The CT component was carried out without intravenous or oral contrast. Imaging data were reconstructed with a standard filter into transaxial slices with a field of view of 50cm, a matrix size of 512×512 and a slice thickness of 2.5mm. CT was followed immediately by PET, using a standard whole body acquisition protocol from the skull vertex to the midthigh level. The scan field of view was 70cm. Attenuation correction was performed from the CT. The PET data were reconstructed into transaxial slices with a matrix size of 192×192 and a slice thickness of 3.3mm, displayed in coronal, transverse and sagittal planes.

Prior to 2009, progression of liver lesions was evaluated in accordance with the original Response Evaluation Criteria in Solid Tumours (RECIST) guidelines.¹⁵ Following 2009, RECIST version 1.1 was used instead.¹⁶ Indeterminate liver lesions were deemed malignant based on radiological and/or histological criteria that would satisfy the diagnosis of CRLM.

Surgery

Liver transection was carried out using the Cavi-Pulse ultrasonic surgical aspirator (Valley Lab, Boulder, CO, US). Intraoperative ultrasonography was used to confirm the location of malignant lesions on preoperative imaging and to identify major vascular pedicles prior to parenchymal transection. Type of surgical procedure was dependent on the resection of all macroscopic disease and achieving a clear resection margin while preserving sufficient liver remnant.

Patients who had indeterminate liver lesions on CT that were then diagnosed or suspected to be CRLM on another imaging modality were considered for hepatic resection. This was also the case for patients with indeterminate liver lesions on CT that were deemed resectable during the follow-up period based on location and number of lesions.

Follow-up review

Following the initial outpatient review at 1 month, all patients were assessed at 3, 6, 12, 18 and 24 months, and on an annual basis thereafter. At each clinical visit, serum CEA levels were measured. All patients were followed up for a minimum of one year from liver resection for CRLM.

Surveillance imaging included CT of the thorax, abdomen and pelvis on a six-monthly basis for the first two years, with annual CT thereafter. MRI was used to elucidate suspicious hepatic lesions that were not fully characterised on CT. Development of symptoms suggesting recurrence between usual follow-up visits usually warranted earlier review than planned. In cases where recurrence was detected on

surveillance imaging, individuals with non-resectable disease were referred for palliative chemotherapy while those eligible for further surgery had an expedited liver and/or lung resection following discussion in appropriate MDT meetings.

Statistical analysis

A chi-squared test was employed to assess the clinicopathological differences between the benign and malignant liver lesions. Statistical analysis was performed using SPSS® version 16.0 (SPSS, Chicago, IL, US). A *p*-value of <0.05 was considered statistically significant.

Results

During the study period, 56 patients (31 male) with a background of CRC were found to have indeterminate liver lesions on CT. The median age was 65 years (range: 36–86 years). There were 33 patients (58.9%) with solitary indeterminate lesions. Twenty-seven patients (48.2%) had their primary colorectal cancer in situ when referred to the specialised MDT (Table 1).

Following discussion at the MDT meeting and review of the CT, 53 patients (94.6%) underwent supplementary imaging. Fifty of these had MRI of the liver and three had PET-CT as there was suspicion of distant extrahepatic disease (Fig 1). The remaining three patients had subsequent interval CT of their indeterminate liver lesions.

With respect to the 50 patients who had further investigation with MRI, 8 were diagnosed with CRLM, 19 had

lesions compatible with benign growths (hepatic cysts [*n*=9], haemangiomas [*n*=6], focal nodular hyperplasia [*n*=2], area of fatty change/perfusion defect [*n*=2]) and 23 patients remained indeterminate following the initial MRI. Two patients subsequently underwent liver resection for a high index of suspicion for the presence of CRLM following MDT discussion and their histopathological analysis confirmed the diagnosis of CRLM.

The remaining 21 patients who had indeterminate liver lesions on MRI underwent interval imaging with either CT or MRI (median: 9 months, range: 3–52 months). Following this, 14 of these patients were considered to have stable lesions (therefore assumed to be benign) and continued to have surveillance imaging whereas 7 patients had evidence of progression on interval imaging consistent with metastatic disease. Six of these seven patients underwent liver resection demonstrating histopathologically proven CRLM while the last patient had an ultrasonography guided biopsy of an atypical liver lesion, which confirmed a focus of a hepatocellular carcinoma.

There were six patients from the total cohort of 56 patients who did not have MRI following the diagnosis of indeterminate liver lesion on CT. Three patients were investigated with PET-CT. In two of these cases, there were features suggesting liver metastases and so these patients underwent liver resection. In the last patient, there was no avid uptake on PET-CT and the lesion was considered benign. The remaining three patients had interval CT performed between three and six months after the initial staging CT. This showed progression consistent with metastatic disease in two patients, who proceeded with liver resection, which confirmed CRLM, while the last patient had a stable lesion, which was therefore deemed benign.

Overall, in 20 (35.7%) of the 56 patients diagnosed with indeterminate liver lesions following CT, these were found to be secondary to CRLM. Patients aged ≥65 years were significantly more likely to have underlying malignancy in these indeterminate lesions (*p*=0.002) (Table 1). Other clinicopathological factors did not reveal any significant differences between patients with stable (benign) lesions and those with malignant lesions on follow-up imaging that could predict the ‘malignant’ nature of these indeterminate liver lesions.

Discussion

The outcome following hepatic resection for CRLM depends on adequate tumour clearance after establishing an accurate assessment of the true extent and stage of the disease. Multiple studies have shown improved survival following treatment by surgical resection of hepatic metastasis.^{17,18}

Suboptimal staging of the disease will often result in futile, unnecessary laparotomies and high incidences of early disease recurrence despite achieving a clear resection margin. This suggests that there are a considerable number of occult lesions that are not identified on preoperative imaging or erroneously labelled as benign that will subsequently show evidence of progression and influence the

Table 1 Statistical analysis of clinicopathological factors in patients with benign and malignant lesions on computed tomography

Clinicopathological factors	Benign (n=35)	Malignant (n=21)	<i>p</i> -value
Age ≥65 years	12 (34.3%)	16 (76.2%)	0.002
Male sex	20 (57.1%)	11 (52.4%)	0.729
Synchronous presentation	17 (48.6%)	10 (47.6%)	0.945
Rectal cancer	10 (28.6%)	5 (23.8%)	0.697
CEA >5µg/l*	3/21 (14.3%)	4/17 (23.5%)	0.465
CRP >10mg/l*	10/16 (62.5%)	10/15 (66.7%)	0.809
NLR ≥5*	3/27 (11.1%)	3/18 (16.7%)	0.591
PLR ≥150*	13/27 (48.1%)	13/18 (72.2%)	0.109
Indeterminate lesions			0.440
Solitary	22 (62.9%)	11 (52.4%)	
Multiple	13 (37.1%)	10 (47.6%)	

CEA = carcinoembryonic antigen; CRP = C-reactive protein; NLR = neutrophil-to-lymphocyte ratio; PLR = platelet-to-lymphocyte ratio
*Results not available for all patients

overall survival of these patients. The preoperative diagnostic workup is therefore an important part of the management of CRC patients so as to correctly identify liver metastases.

These patients include those with bilobar liver disease that can be subjected to downstaging therapy and who could later could undergo liver resection with curative intent.⁵

In the UK, the guidelines for staging of CRLM suggest patients have staging CT of the thorax, abdomen and pelvis as well as MRI of the liver.¹⁹ This is supported by a study that showed better sensitivities with MRI in detecting liver metastasis in up to 84.9% of the cases compared with 69.2% following conventional CT.²⁰

Zech *et al* published the results of a randomised multi-centre trial that showed that CT as a single imaging modality resulted in changes in surgical planning in 47% of patients undergoing surgery, which suggests inadequate staging of the disease.²⁰ The authors also observed an improved diagnostic confidence of 98.3% and 85.7% following the use of liver specific contrast agents such as gadoxetic acid derivatives in enhanced MRI and conventional MRI respectively. Other studies have also demonstrated that contrast enhanced MRI has the ability to provide better anatomical details, especially in patients who undergo neoadjuvant treatment, which usually modifies the underlying liver parenchyma owing to vascular changes and/or hepatic steatosis.^{21,22}

In the present study, MRI was an important adjunct to initial staging CT as it led to a radiological diagnosis in 54.0% of cases that were found to be indeterminate on CT. Over a third (34.8%) of patients who had liver lesions that remained indeterminate following MRI were eventually found to have liver metastasis. This suggests that a considerable proportion of these small, initially quiescent lesions harboured foci of malignancy. It is important to counsel patients with regard to this, and to have a low threshold for the suspicion of CRLM and (where appropriate) consider liver resection in these patients. Moreover, this highlights the importance of continued radiological surveillance in patients with CRC to identify these metastatic lesions at an early stage and re-refer them to specialist centres for appropriate management.

The role of PET in the management of CRLM is currently reserved for detecting local recurrence following CRC resections and identifying the presence of distant metastasis, with a reported sensitivity and specificity of 88.0% and 96.1% respectively for detecting CRLM.²³ PET-CT provides both anatomical and functional assessment that has proved to be valuable (especially in equivocal cases) owing to its ability to locate sites of occult metastasis.^{24,25} Nevertheless, the technology has its own limitations with false positive results in the presence of local inflammation and/or infection, and false negative results in isometabolic metastasis that does not demonstrate avid fludeoxyglucose uptake.

Yip *et al* demonstrated that the adoption of upfront triple assessment using CT, MRI and PET-CT decreased the number of futile laparotomies.²⁶ However, conducting all three imaging modalities on all patients is not feasible, and would result in treatment delays and increased healthcare costs. Recently, our unit started to adopt a selective approach with the use of PET-CT in cases with inconclusive MRI in conjunction with assessment of serum CEA; this approach is weighed against the option of interval MRI after achieving a consensus opinion by MDT members.

Previous studies have noted an association between tumour biology and a patient's systemic inflammatory response to tumours such as raised CRP, NLR and PLR in CRLM.^{11–15} The present series showed that there were no significant differences between the benign and malignant liver lesions that were indeterminate on CT with respect to elevated CRP, NLR or PLR. CEA levels are currently used in postoperative surveillance following resection of CRC and CRLM.²⁷ In our study, a raised serum CEA level did not assist in predicting underlying malignancy in these indeterminate liver lesions.

The current study also attempted to elucidate clinicopathological variables that could assist in predicting underlying malignancy in indeterminate hepatic lesions. There was a significant association in patients aged ≥ 65 years between indeterminate liver lesions on CT and malignancy. This suggests that in older patients who have indeterminate liver lesions on CT, there should be a low threshold for suspecting an underlying malignancy.

Our study has its own limitations resulting from the small sample size and being a single unit experience. Our unit does not routinely obtain confirmation of diagnosis with image guided biopsy of benign or possibly malignant lesions owing to the risks of false sampling results, especially with these small lesions and the feared risks of mechanical and oncological complications.²⁸ A large, multicentre, prospective study is required to address this important clinical dilemma. Nevertheless, despite the improved technology of current imaging modalities, there will be a relatively small subgroup of patients whose liver lesions will remain indeterminate following both CT and MRI. These patients should be considered for PET-CT. An algorithm for managing such patients has been proposed (Fig 2). Patients who have liver lesions that remain indeterminate should be counselled for liver resection, when appropriate.

Conclusions

All patients with indeterminate liver lesions on CT with a background of CRC should be offered MRI of the liver to characterise these lesions further. Over a third of lesions deemed indeterminate following CT in our study progressed and showed evidence of CRLM. Patients aged ≥ 65 years should be counselled with regard to the appropriateness of proceeding with a resectional strategy rather than interval surveillance.

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