Outcomes in patients with indeterminate pulmonary nodules undergoing resection for colorectal liver metastases

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Abstract

Objectives: This study aimed to assess outcomes in patients who underwent hepatic resection for colorectal liver metastases (CRLM) with subcentimetre indeterminate pulmonary nodules (IPN) and to devise a management pathway for these patients.

Methods: Patients undergoing CRLM resection from January 2006 to December 2010 were included. Survival differences following liver resection in patients with and without IPN were determined.

Results: A total of 184 patients were included, 30 of whom had IPN. There were no significant differences between the IPN and non-IPN groups in terms of demographics, surgery and pathological factors. There were no significant differences between patients with and without IPN with respect to disease-free (P = 0.190) and overall (P = 0.710) survival. Fifteen patients with IPN progressed to metastatic lung disease over a median period of 10 months (range: 3–18 months); six of these patients underwent lung resection. Of the remaining 15 patients with IPN, eight showed no IPN progression and subsequent CT scans did not identify IPN in the remaining seven.

Conclusions: Colorectal liver metastases patients with IPN who have resectable disease should be treated with liver resection and should be subject to intensive surveillance post-resection. Although 50% of these patients will progress to develop lung metastases, this does not appear to influence survival following liver resection.

Keywords

hepatectomy, hepatic resection, liver metastases, colorectal cancer, lung nodules, survival

Received 15 February 2012; accepted 24 March 2012

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Introduction

Hepatic resection has become the treatment of choice in resectable colorectal liver metastasis (CRLM) and is associated with longterm survival in these patients. Around 25% of patients have synchronous liver metastases at presentation and a further 20% subsequently develop metachronous liver disease, usually within 2 years of resection of the primary tumour.1–3 Despite the variability in the selection criteria of patients with CRLM for hepatic resection, 5-year survival rates of up to 58% have been reported.4–9

Current preoperative staging of patients with suspected CRLM and surveillance protocols following the resection of colorectal primary disease includes computed tomography (CT) of the thorax, abdomen and pelvis.10 The main aim is to determine the extent of disease, including intra- and extrahepatic disease because management strategies for these patients range from potentially curative hepatic and/or lung resection to palliative chemotherapy. Following the detection of CRLM, most hepatobiliary units will also perform magnetic resonance imaging (MRI) of the liver to elucidate further smaller liver metastases
not demonstrated on CT. A major role of contrast-enhanced CT imaging is to identify sites of extrahepatic disease in lymph nodes, peritoneum and lungs, which can potentially alter the management strategy in these patients.

In addition, preoperative CT scans may detect subcentimetre indeterminate pulmonary nodules (IPN) in patients with resectable CRLM. It can be difficult to interpret these findings as IPN can be found in up to 25% of the general population.\cite{11} The presence of extrahepatic disease has traditionally been regarded as a contraindication for liver resection because it has been associated with poorer outcomes.\cite{12} Because of the characteristics of IPN, further diagnostic imaging, such as positron emission tomography (PET), has been suggested in some studies.\cite{9,11} However, the small size of IPN means that PET may fail to differentiate metastatic disease from a benign inflammatory process. To date, there is no consensus view on whether these patients should be managed using further imaging prior to hepatic resection, by delaying or abandoning hepatic resection, or by proceeding with hepatic resection and intensive postoperative surveillance.

The aim of this study was to assess outcomes in patients who underwent potentially curative hepatic resection for CRLM with IPN. The secondary aim was to devise a management pathway for these patients.

### Materials and methods

#### Patients

Patients with CRLM undergoing hepatic resection at the Hepatobiliary and Pancreatic Unit, Queen’s Medical Centre (QMC), Nottingham University Hospitals National Health Service (NHS) Trust, Nottingham, UK, during the 5-year period from January 2006 to December 2010, were identified from a prospectively maintained hepatobiliary database. Patients who underwent primary hepatic resection with curative intent in the presence of subcentimetre IPN during the study period were included in the analysis. Patients with pulmonary nodules that were characteristic of malignant lesions, benign calcified lesions or granulomas were excluded from this study.

Collated data included patient demographics, laboratory analyses, types of surgical resection, histopathology analyses and clinical outcomes. Preoperative radiological assessment included a CT scan of the thorax, abdomen and pelvis, and MRI of the liver. Contrast-enhanced images of the thorax, abdomen and pelvis were obtained using multi-row detector CT scanners with collimation of 2.0–0.625 mm using standardized protocols. The scans were performed from just above the superior aspect of the lungs to below the ischial tuberosities. Contiguous axial images with a thickness of 1.5–8.0 mm were reconstructed from the data. Oral contrast medium was accompanied by 100 ml i.v. contrast administered through a peripheral vein at an average rate of 3 ml/s (Niopam 300; Bracco UK Ltd, High Wycombe, UK). All preoperative and subsequent surveillance CT scans documenting IPN were reviewed by a consultant radiologist (WKD) with an interest in hepatobiliary radiology.

Radiologic characteristics of IPN were assessed with respect to number, size and laterality. Prior to 2009, IPN progression was determined using RECIST (response evaluation criteria in solid tumours) Version 1 criteria.\cite{13} Since 2009, RECIST Version 1.1 criteria have been used.\cite{14} Indeterminate pulmonary nodules were considered to be malignant based on a radiological and/or histological diagnosis of malignancy, both of which satisfy the diagnostic criteria for metastatic pulmonary disease in colorectal cancer.

#### Surgery

Parenchymal transection was performed using the Cavi-Pulse ultrasonic surgical aspirator (CUSA®; Model 200T, Valley Lab., Boulder, CO, USA). Intraoperative ultrasound was performed to confirm the findings of preoperative imaging and to assist in surgical planning. The number of hepatic (Couinaud)\cite{15} segments resected was determined by the procedure performed as stated using the Brisbane nomenclature.\cite{16} Type of surgical procedure was dependent on the resection of all macroscopic disease and on achieving a clear resection margin while preserving sufficient remnant liver. The extent of hepatic resection in this study was classified under two categories according to whether the procedure involved less than a hemi-hepatectomy, or a hemi-hepatectomy or more.

All patients with IPN were declared to show pulmonary metastases during the follow-up period and were deemed to be resectable based on the location and number of metastases. These patients were referred to the thoracic surgery department for consideration of resection.

#### Follow-up

Patients were followed up in specialist hepatobiliary clinics. Following an initial postoperative review at 1 month, all patients were examined in outpatient clinics at 3, 6, 12, 18 and 24 months and annually thereafter. At each clinical review, carcinoembryonic antigen (CEA) levels were assessed. All patients in this study underwent follow-up for a minimum of 1 year following hepatic resection for CRLM.

Surveillance imaging included CT scans of the thorax, abdomen and pelvis. Patients underwent 6-monthly CT scans during the first 2 years postoperatively, followed by annual CT scans thereafter. Liver MRI was used to characterize suspicious hepatic lesions demonstrated on CT. The development of symptoms of recurrence at any time-point prompted an earlier review than scheduled.

Following detection of recurrences on surveillance imaging, all patients were discussed in a multidisciplinary meeting that included hepatobiliary surgeons, an oncologist, a radiologist and a pathologist. Patients with non-resectable disease were referred to the oncologist and patients who were suitable for further surgery underwent liver and/or lung resection within an average of 4 weeks. Overall and disease-free survival data were recorded. Disease-free survival was defined as the time from primary hepatic resection to the first documented recurrence of disease on imaging. Overall survival was defined as the time between the date...
of primary hepatic resection and the date of death or most recent
date of follow-up if the patient was still alive.

Statistical analysis
Categorical data were presented as frequencies and percentages.
The Kaplan–Meier method was used to assess actuarial survival
and disease-free survival. Statistical analyses were performed
using SPSS Version 16.0 (SPSS, Inc., Chicago, IL, USA). Statistical
significance was taken at the 5% level.

Results
Patient demographics, surgical procedures and pathological data
During the study period, 184 patients underwent primary hepatic
resection for CRLM at QMC, of whom 30 (16.3%) demonstrated
IPN on preoperative staging CT. The majority of patients in this
study were male (n = 113, 61.4%). Synchronous disease was
present in 74 (40.2%) patients. Six (3.3%) patients underwent
neoadjuvant oxaliplatin-based chemotherapy prior to liver resec-
tion. Demographics and clinical factors with respect to the pres-
ence of IPN are summarized in Table 1. Major hepatic resection
(hepatectomy or more) was performed in 92 (50.0%) patients,
with no postoperative deaths. Negative margin (R0) resection
was achieved in 145 (78.8%) patients.

During the study period, 54 (29.3%) patients died of recurrent
disease. The median follow-up period in the remaining patients
was 27 months (range: 12–71 months).

Indeterminate pulmonary nodules
Staging CT showed IPN in 30 (16.3%) patients. No significant
differences in demographics, extent of hepatic resection, R0 resec-
tion rate, or size and number of liver metastases were observed in
patients with and without IPN. The majority of patients had
only one IPN (n = 25, 83.3%). Three patients had two IPNs and
two patients had more than two IPNs. Two (6.7%) patients had
bilateral IPN.

Of the 30 patients in whom IPN was detected on preoperative
CT imaging, six (20.0%) underwent further diagnostic imaging in
the form of a PET scan (Fig. 1). However, none of these six patients
showed an increase in uptake of the IPN significant
enough to suggest lung metastasis. In three of these six patients,
progression of the IPN during surveillance was apparent. These
patients were treated with lung resection (n = 1) and palliative
chemotherapy (n = 2). The other three patients did not show any
disease progression of IPN.

Of the 24 patients who did not undergo a pre-liver resection
PET scan, 12 (50.0%) demonstrated progression of IPN, two of
whom showed liver disease recurrence. Five of the 10 patients in
whom IPN progressed without liver recurrence underwent lung
resection and metastatic lung disease was confirmed by histology.

Overall, 50.0% (n = 15) of patients with IPN were ultimately
identified as having metastatic lung disease over a median period
of 10 months (range: 3–18 months); six of these patients (40.0%)
underwent lung resection. All of the lesions that progressed
were found to represent lung metastases. Nine patients with IPN
identified as metastases were inoperable as a result of the number
and location of metastases, and were treated with palliative
chemotherapy.

In the remaining 15 (50.0%) patients, no progression of IPN
was observed in eight patients and no IPN was identified on
surveillance imaging in seven patients over a median follow-up of
27 months (range: 12–64 months). Of note, none of the eight
patients in whom IPN did not progress underwent lung resection.

Disease recurrence and survival
In this cohort of 30 patients with IPN, median disease-free and
overall survival were 17 months and 25 months, respectively. Rates
of 1-, 3- and 5-year disease-free survival in patients with IPN were
56.3%, 31.4% and 31.4%, respectively. Of the 154 patients without
IPN, 71 (46.1%) patients remained disease-free. Rates of 1-, 3- and
5-year disease-free survival in patients without IPN were 70.5%,
41.4% and 35.0%, respectively. There was no significant difference

Table 1 Demographic, clinical and pathological factors in patients with and without indeterminate pulmonary nodules (IPN) (n = 184)

<table>
<thead>
<tr>
<th>Demographic, clinical and pathological factors</th>
<th>No IPN (n = 154)</th>
<th>IPN (n = 30)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic factors, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥65 years</td>
<td>88 (57.1%)</td>
<td>18 (60.0%)</td>
<td>0.772</td>
</tr>
<tr>
<td>Male gender</td>
<td>97 (63.0%)</td>
<td>16 (53.3%)</td>
<td>0.320</td>
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<tr>
<td>Synchronous presentation</td>
<td>58 (37.7%)</td>
<td>16 (53.3%)</td>
<td>0.109</td>
</tr>
<tr>
<td>Extent of resection, n (%)</td>
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<td></td>
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</tr>
<tr>
<td>Hemi-hepatectomy or more</td>
<td>73 (47.7%)</td>
<td>19 (63.3%)</td>
<td>0.118</td>
</tr>
<tr>
<td>Histopathological factors, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Largest tumour size ≥5 cm</td>
<td>47 (30.5%)</td>
<td>12 (40.0%)</td>
<td>0.309</td>
</tr>
<tr>
<td>Solitary hepatic metastases</td>
<td>77 (50.0%)</td>
<td>17 (56.7%)</td>
<td>0.504</td>
</tr>
<tr>
<td>Resection margin [R0 (≥1 mm)]</td>
<td>124 (80.5%)</td>
<td>21 (70.0%)</td>
<td>0.197</td>
</tr>
</tbody>
</table>
in disease-free survival between the IPN and non-IPN groups ($P = 0.190$) (Fig. 2).

One-, 3- and 5-year overall survival rates in patients without IPN were 94.7%, 65.1% and 48.1%, respectively; those in patients with IPN were 90.0%, 59.0% and 50.5%, respectively. There were no significant differences in overall survival between the two groups ($P = 0.710$) (Fig. 3).

**Discussion**

At present, hepatic resection in combination with systemic chemotherapy is the treatment modality of choice for CRLM. Nevertheless, hepatic resection in the presence of concomitant extrahepatic disease is associated with a poorer outcome, particularly in patients with peritoneal or portal lymph node disease. However, resection of pulmonary colorectal metastases has been associated with improved longterm survival, particularly in patients with a solitary metastasis that is suitable for anatomical resection.

Improvements in CT imaging have increased findings of IPN in patients with resectable CRLM, although the clinical significance of these findings remains to be determined. In a series of 439 patients with resectable primary colorectal cancer, Brent et al. observed that only five (11%) of 45 patients in whom indeterminate lung lesions were shown on preoperative CT prior to resect-

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**Figure 1** Outcomes in patients undergoing initial hepatic resection and surveillance with respect to the presence of indeterminate pulmonary nodules (IPN). CRLM, colorectal liver metastasis; PET, positron emission tomography

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**Figure 2** Differences in disease-free survival in patients with and without indeterminate pulmonary nodules (IPN)
disease in the colorectal primary tumour and the absence of calcification on lung nodules. With respect to the size of lung nodules, previous studies have shown that solitary nodules and nodules measuring ≥10 mm are more likely to be malignant, and nodules sized ≤5 mm are usually benign in patients with known malignancy. The present study included only CRLM patients with IPN of <10 mm and without benign features such as calcification, and hence specific features such as size and the presence of calcification are not relevant in determining the progression of these lung lesions. In addition, the majority of patients in this study had solitary pulmonary lesions.

Positron emission tomography has been used in some centres for preoperative staging prior to hepatic resection. Fernandez et al. reported a 5-year overall survival rate of 58% following hepatic resection for CRLM in patients who underwent preoperative staging with PET. At present, the published data available to determine the role of PET in the evaluation of subcentimetre IPN are limited. Given that the threshold resolution of current PET scanners is only 5–6 mm, it is unlikely that PET will provide useful information on lung lesions that measure <5 mm. With respect to lung nodules sized 5–10 mm, an increase in the uptake of these lesions in PET is likely to indicate metastatic disease. However, a negative PET result does not conclusively rule out underlying metastases. O and colleagues observed that of 121 patients with small pulmonary nodules that had minimal or no uptake on PET imaging, 24 (20%) patients had underlying non-thoracic malignancy. Previous studies have shown the progression of pulmonary disease following hepatic resection for CRLM despite a negative PET scan. In the current study, only six patients underwent preoperative PET imaging prior to liver resection, and none of them demonstrated IPN uptake suggestive of lung metastases. Of these six patients, three patients subsequently did experience progression of IPN suggestive of metastatic disease; two were managed with palliative chemotherapy and the other underwent lung resection. These results suggest that the role of PET imaging in the evaluation of subcentimetre IPN remains to be determined.

Because of the difficulty in determining whether IPN may represent metastatic lung disease, the issue of whether patients should be offered potential curative liver resection is controversial. It is currently not acceptable to subject patients with resectable CRLM to biopsy of the IPN as the small size of the latter poses considerable challenges in attempts to obtain an accurate biopsy by fine-needle aspiration or video-assisted thoracoscopic surgery. This practice may be associated with a high sampling error, risk for seeding of tumour cells and morbidity related to these procedures. Furthermore, in this study 50.0% of IPN cases were not malignant. The present study showed no statistically significant differences with respect to disease-free and overall survival between patients with and without IPN. Furthermore, there were no significant differences in clinical, surgical and pathological factors between the two groups of patients. This finding suggests that the presence of IPN should not preclude patients with resectable hepatic metastases from undergoing liver resection. This study
also emphasizes the importance of surveillance post-liver resection because the progression of IPN can be detected and a subgroup of patients will have resectable lung disease that can be potentially cured.

There are currently no guidelines for managing IPN in patients with resectable CRLM. Because IPN is a common finding, an algorithm for managing these patients has been proposed (Fig. 4). In the present study, half of all patients with IPN ultimately progressed to metastatic lung disease, which suggests that this group of patients requires intensive surveillance post-surgery. This practice can be justified as a subgroup of these patients will be suitable for lung resection with curative intent. As the clinical variables and radiological characteristics that help to differentiate benign from malignant IPN in CRLM patients are limited, these patients should be offered liver resection and should undergo an intensive surveillance protocol as their survival is not significantly affected by the presence of IPN.

Conflicts of interest
None declared.

References


