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HPB

ORIGINAL ARTICLE

Detailed liver-specific imaging prior to pre-operative chemotherapy for colorectal liver metastases reduces intra-hepatic recurrence and the need for a repeat hepatectomy

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Abstract

Background: Neoadjuvant chemotherapy for colorectal liver metastases (CRLM) reduces the accuracy of liver imaging which may understage patients pre-operatively. Retrospective review of a prospective database to determine whether liver-specific magnetic resonance imaging (MRI) prior to pre-operative chemotherapy affects intra-hepatic recurrence and long-term outcome after hepatectomy.

Patients and methods: Between 2003 and 2009, 242 patients with CRLM underwent a hepatectomy after ≥3 cycles of oxaliplatin or irinotecan-based chemotherapy. All had a liver-specific MRI immediately pre-operatively. The outcome of patients who had a liver-specific MRI prior to chemotherapy (PCI group, $n = 92$) was compared with those who did not (non-PCI group, $n = 150$).

Results: A liver-specific MRI pre-chemotherapy changed the staging in 56% of patients. At a median (range) follow-up of 55 (6–94) months, there was a higher incidence of intra-hepatic recurrence at a new site in the non-PCI group (65% vs. 48% in the PCI group, $P = 0.041$) and an increased rate of recurrence in patients with the same number of lesions pre- and post-chemotherapy [hazard ratio (HR) 2.02, 1:10–3.37, $P = 0.024$]. The non-PCI group underwent more repeat hepatectomies than the PCI group (24.7% vs. 13%, $P = 0.034$), achieving similar long-term survival.

Conclusions: A liver-specific MRI prior to chemotherapy reduces intra-hepatic recurrence and avoids a repeat hepatectomy.

Keywords

colorectal metastases < liver, chemotherapy < liver, hepatectomy, magnetic resonance imaging of liver

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Introduction

Colorectal cancer is common, with 39 991 new cases diagnosed in the UK in 2008 alone.[1] Of these patients, 15–20% will present with colorectal liver metastases (CRLM)[2] and a further 40–50% will develop CRLM within 3 years of successful resection of their primary tumour.[3] Hepatic resection offers the best chance of long-term survival, with 5-year survival rates of 37–50%.[4–7]

Neoadjuvant and conversion chemotherapy is increasingly being used not only to render previously unresectable patients resectable[8,9] but to improve overall progression-free survival.[10] However, chemotherapy can alter the image characteristics of hepatic metastases, with some lesions undergoing cystic transformation and others showing a complete radiological response and disappearing.[11] Such disappearing metastases will inevitably reappear over time.[12] Chemotherapy can also damage the background liver parenchyma, causing steatosis, steatohepatitis or sinusoidal dilatation,[13] with consequent alteration of the radiological characteristics of the background liver parenchyma[14,15] and less accurate radiological detection of metastases.[11]

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Magnetic resonance imaging (MRI) with liver-specific contrast agents is currently the gold standard for intra-hepatic staging of CRLM.[16,17] The aim of the present study was to compare the outcome of patients undergoing liver resection for CRLM after pre-operative chemotherapy who underwent liver-specific MRI prior to starting chemotherapy (PCI group) with those patients who were not subject to an initial liver-specific MRI (non-PCI group). The primary objective was to compare the incidence of intra-hepatic recurrence in both groups. Secondary outcomes were overall survival and the incidence of re-intervention for disease recurrence in the liver.

Materials and methods

Patient selection

A retrospective review of a prospective computer database (Access®; Microsoft Corporation, Redmond, WA, USA), containing all liver resections for CRLM at a tertiary referral institution from 1 June 2003 to 1 December 2009, was undertaken to identify all those who underwent resection of CRLM after chemotherapy. The start date coincided with the introduction of contrast-enhanced MRI for intra-hepatic staging. The database provided a comprehensive dataset consisting of 268 data fields compiled contemporaneously from a standardized pro forma, which encompassed patient symptoms, pre-operative assessment, surgical treatment, postoperative course, histopathology and long-term adverse outcomes.

Pre-operative staging

All patients underwent contrast-enhanced computerized tomography (CT) scanning of the chest, abdomen and pelvis. Patients were defined as having synchronous metastases if they presented with secondaries at the same time or within 3 months of their primary tumour, even if subsequent liver resection was delayed by chemotherapy or treatment of the primary. Liver metastases presenting outside of this time frame were regarded as metachronous or delayed. Patients with indeterminate or unfavourable factors such as extensive lymph node involvement or T4 primary tumours were considered for staging laparoscopy with laparoscopic ultrasonography. Positron emission tomography-CT (PET-CT) was performed in an attempt to confirm or refute concerns regarding extra-hepatic disease.

Indications for chemotherapy

Neoadjuvant or conversion chemotherapy was given either for known resectable CRLM or to 'downstage' initially inoperable CRLM, respectively. Only patients who had completed at least three cycles of oxaliplatin or irinotecan-based regimens were included.

MRI Protocol and patient groups

All patients underwent a liver-specific contrast-enhanced MRI prior to surgery. Radiological assessment was undertaken using a Symphony 1.5-T magnet (Siemens, Munich, Germany) supplemented by intravenous (i.v.) contrast agents and delayed phase scans. The contrast agents used were initially Ferucarbotran (Resovist®; Bayer Schering Pharma, Switzerland) and gadodiamide (Omniscan®; Amersham Health, Oslo, Norway), but since 2005, gadoxetic acid (Primovist®; Bayer Schering Pharma, Switzerland) and Gadobutrol (Gadovist®; Bayer Schering Pharma, Switzerland) have been used. The radiological protocol has been described previously.[18]

The patient cohort was divided into two groups on the basis of their imaging prior to liver resection. Patients in the pre-chemotherapy imaging group (PCI) had a double-contrast MRI scan of the liver prior to commencing chemotherapy (or within the first 2 weeks) and a second similar MRI scan just prior to surgery. Patients in the non-PCI group did not have a double-contrast liver MRI prior to commencing chemotherapy, having liver staging with contrast-enhanced CT or a single or non-contrast enhanced MRI instead. All these patients had a double-contrast MRI prior to surgery.

Many patients were referred from other institutions. If they were referred prior to commencing chemotherapy, liver-specific imaging was undertaken at Basingstoke using our MRI protocol. Otherwise pre-chemotherapy imaging was obtained from the referring unit. Since March 2006, all radiology has been downloaded onto an intranet imaging database (Centricity Enterprise Web V3.0; GE Medical systems, 1995–2006, Chalfont St Giles, Buckinghamshire, UK). Prior to this date, hard copy films were obtained. An assessment of the quality of all MRI scans from referring centres was undertaken independently, by two hepatobiliary surgeons (M.R. and F.W.), to allow final group allocation. MRI scans with single or no contrast agents were deemed inadequate and these patients were placed in the non-PCI group.

Details of the radiological CRLM distribution both pre- and post-chemotherapy were documented. In addition, those patients in the PCI group had their response to chemotherapy assessed according to the response evaluation criteria in solid tumours (RECIST) criteria.[19]

Liver surgery

Fitness for liver surgery was assumed by survival from a colorectal resection and/or a willingness to proceed regardless of age. Resectability for cure in all patients required complete resection of all liver metastases, regardless of size, number, distribution or width of resection margin, while preserving a sufficient volume of functioning liver parenchyma (usually greater than 25–30% of normal liver parenchymal volume as estimated by MRI[20]). It is our philosophy to resect all known sites of disease seen on the original scans. All patients undergo intra-operative ultrasound (IOUS) at the time of resection. For lesions that have undergone a complete radiological response an intensive search using palpation and IOUS is made. If the area can be removed by an anatomical segmental resection leaving a viable volume of functioning liver this is performed. However, on occasions when a blind resection would endanger key biliary/vascular structures or leave an insuf-

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ficient volume of residual liver, we have elected to closely observe the site of disease and treat any recurrence when it occurs.

The anaesthetic and surgical techniques specific to both primary and repeat hepatic resection have been described in detail previously.[20–22] The nomenclature and extent of hepatic resection were recorded according to the terminology defined by Couinaud and, more recently, the Terminology Committee of the International Hepato-Pancreato-Biliary Association.[23] A major resection was defined as a resection of three or more segments.

Post-operative follow-up

Every patient underwent 6-monthly measurement of serum carcinoembryonic antigen (CEA) and CT scanning of the chest, abdomen and pelvis for 3 years, then annually for 10 years. A colonoscopy was performed at 2 years. If recurrent disease occurred, assessment for repeat resection was undertaken. Up-to-date survival and disease status were confirmed on a 6-monthly telephone audit by database staff. No patient was lost to follow-up.

Outcome measures

The primary outcome measure was the incidence of and time to intra-hepatic recurrence. Secondary outcomes included disease-free and overall survival and the need for repeat liver resection. All outcome measures were taken from the time of the first liver resection.

Exclusions

The patient flow chart and summary of exclusions are presented in Fig. 1 and Table 1. Pre-operative chemotherapy had to be of sufficient potency and duration to elicit a significant effect on the CRLM. Hence, patients had to have completed three or more cycles of oxaliplatin or irinotecan-based chemotherapy. Sub-optimal regimens such as 5-fluorouracil (5-FU) monotherapy or regimens of a shorter duration were excluded. The CRLM had to have been diagnosed and staged either prior to commencement of chemotherapy or before the second cycle. This meant those with CRLM diagnosed during or immediately after adjuvant chemotherapy for their primary were excluded along with those who developed CRLM sometime after adjuvant therapy and then proceeded directly to liver resection without further treatment.

Patients who were inoperable at the time of resection or those that progressed after the first stage of a two-stage hepatectomy were excluded. Four patients with inoperable, large volume disease (>10 CRLM) before chemotherapy were also excluded (two in each group). These patients had exceptional responses to chemotherapy and underwent liver resection after a trial of time, to clear all identifiable sites of disease, knowingly leaving sites of disappearing metastases. Three out of the four patients also underwent concomitant intra-operative ablation. The *in-situ* disappearing lesions were closely observed. As expected, all patients have had early intra-hepatic recurrence and have undergone subsequent resection or ablation.

Statistical analysis

Continuous variables are presented as median (with range) and categorical data presented as frequency and percentages. The Mann–Whitney *U*-test for continuous data and either Pearson's chi-square test or Fisher's exact test for categorical data was used to detect differences between the two group cohorts. Kaplan–Meier curves were plotted to determine the time to hepatic recurrence and survival outcomes and expressed in median and 95% confidence interval. Statistical significance was analysed with the log-rank (Mantel–Cox) test. The Cox proportional-hazard regression analysis was used to analyse the hazard ratio (HR) of the survival distribution to the variables. A *P*-value of less than 0.05 was considered significant. Data were analysed using SPSS software (version 19.0) (IBM SPSS Inc., Chicago, IL, USA).

Results

During the study period, 818 liver resections were undertaken in 715 patients for CRLM with a curative intent. Of these, 242 patients met the study inclusion criteria (Fig. 1).

Patient demographics and tumour characteristics

The demographic and clinicopathological characteristics of the 242 patients are summarized in Table 2. The two groups were similar with respect to age, gender, nodal status of their primary tumour and pre-chemotherapy CEA. The PCI group had a significantly higher median (range) number of CRLM seen on imaging prior to chemotherapy [3 (1–14)] compared with the non-PCI group [2 (1–20], that was no longer significant after chemotherapy. The median (range) size of the largest CRLM pre-chemotherapy was 33 (5–200) mm in the PCI group, similar to that in the non-PCI group [30 (4–130) mm, $P = 0.545$]. Concomitant extrahepatic disease was present in 38 patients (16%) and there was no difference between groups. The median (range) follow-up for these 240 patients was 55 (6–94) months.

Comparison of referral radiology to liver-specific MRI

The modality and quality of pre-chemotherapy imaging is shown in Table 3. The majority of patients in both groups were referred with a CT with i.v. contrast. Twenty patients in the PCI group had a good quality MRI scan performed at the referring centre, compared with none in the non-PCI group.

In the PCI group, three patients were referred directly for a detailed liver MRI scan without a baseline CT scan and 2 of the 20 patients presenting with good quality liver MRIs did not have their CT images available. The referring imaging of a further three patients was incomplete. Thus a comparison of a good quality liver MRI scan to CT scan or poor quality liver MRI scan was possible in 84 of 92 patients. Of these 84 patients, the liver-specific MRI scan identified an additional 109 CRLMs in 39 (46%) patients. Of these 109 additional metastases, 96 were not seen on previous liver imaging and the remaining 13 lesions had been incorrectly regarded as indeterminate. The median (range) size of

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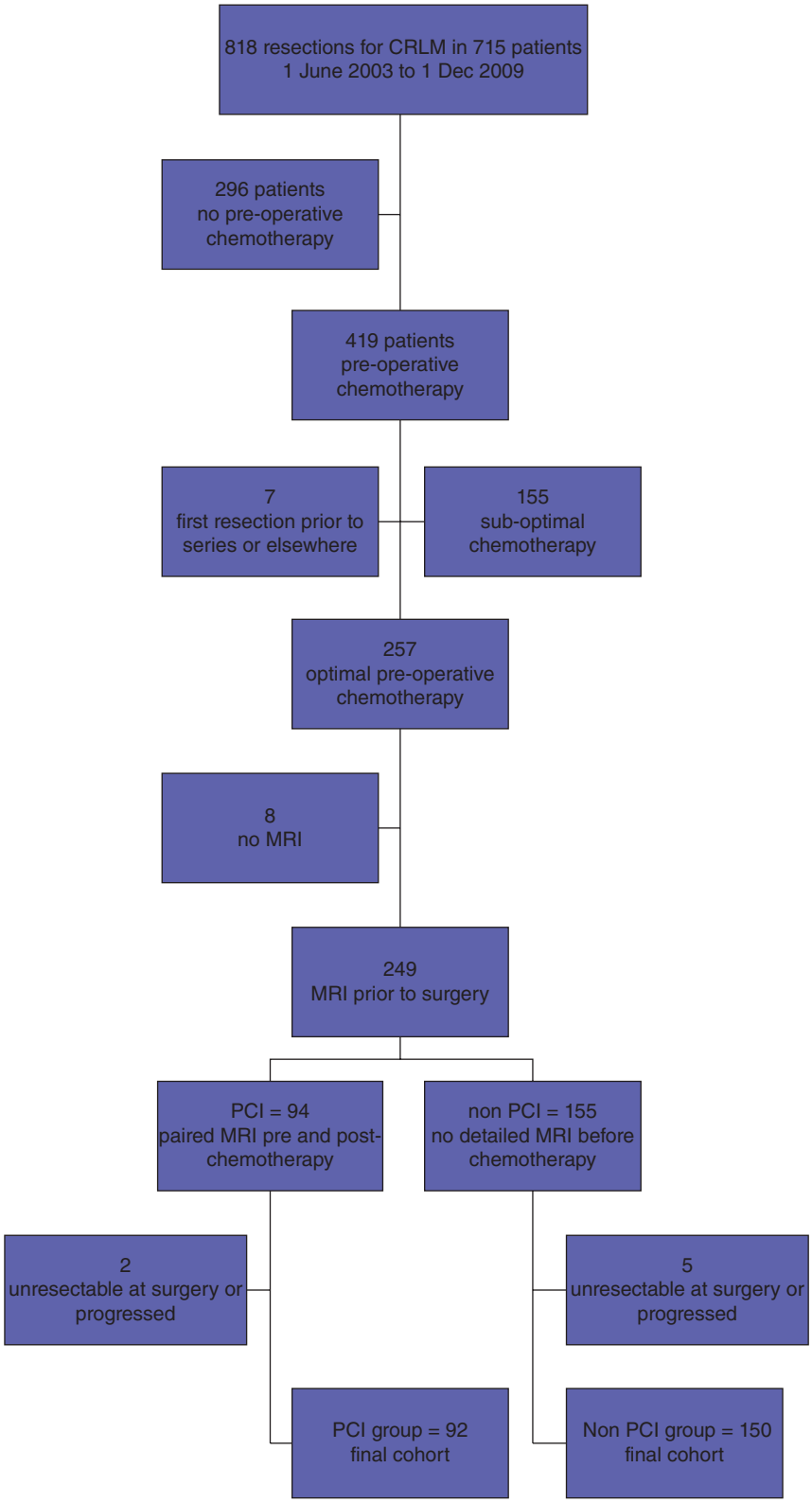

Figure 1 Patient flow chart

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Table 1 Details of excluded patients

Reason for exclusion	Number of patients
Chemotherapy	155
Agent (sub-optimal)	82
Duration (<3 cycles)	55
Timing (no chemotherapy between diagnosis and surgery)	
CRLM detected during chemotherapy	4
Immediately after	4
>12 months after completion	10
No MRI	8
Metal	1
Claustrophobia	3
Unknown	4
Surgical	14
First resection before series or elsewhere	7
Progressive disease after 1st stage liver resection	2
>10 CRLM, known missing lesions (see text)	4
Irresectable at operation	1

CRLM, colorectal liver metastases; MRI, magnetic resonance imaging.

the newly diagnosed CRLM was 8 (4–30) mm. In addition, the liver-specific MRI confirmed the benign nature of 12 indeterminate lesions in a further 9 patients. Overall a good quality liver-specific MRI prior to commencing chemotherapy changed the intra-hepatic staging in 47 of 84 (56%) patients.

The median (range) time interval between scans was 6 (0–54) weeks. Those with longer intervals often had treatment of their primary between imaging. In the two patients with the longest intervals (24 and 54 weeks), re-staging was delayed by post-operative complications after the primary surgery.

Chemotherapy regimens and response

Details of the chemotherapy regimens are shown in Table 4. The majority of patients [n = 219 (90%)] received oxaliplatin-based chemotherapy. Thirty-one (17%) patients were treated with oxaliplatin or irinotecan plus monoclonal antibodies, with no significant difference between the groups. The median (range) number of cycles was six (3–24) and the median (range) time interval between cessation of chemotherapy and liver surgery was 8 (4–99) weeks. Although the median number of cycles was the same between the two groups, the PCI group contained significantly more patients who received just 3–4 cycles of chemotherapy before surgery (37% vs. 19%, $P = 0.003$).

The radiological response to chemotherapy in the liver could be accurately assessed using RECIST criteria[19] for patients in the PCI group, who had paired MRI scans. Eleven patients (12%) progressed, 17 (18%) remained stable, 61 (66%) had a partial response and 3 (3%) had a complete radiological response.

The change in number of CRLM seen on pre- and post-chemotherapy imaging is detailed in Table 4. This shows that the majority of patients [137 (57%)] had the same number of metastases. Thirty-five (14%) patients developed new lesions, with twice as many in the non-PCI group (18%) compared with the PCI group (9%). This just failed to reach statistical significance ($P = 0.059$). Seventy patients (29%) had at least one lesion disappear with chemotherapy. Of this last group, a total of 272 metastases underwent a complete radiological response to chemotherapy. These patients were more likely to have >3 metastases prior to commencing chemotherapy (54%), compared with those whose numbers of metastases remained unchanged (14%) or increased after chemotherapy (32%) $P = 0.001$.

Liver surgery and post-operative course

The details of the liver surgery and post-operative course are shown in Table 5. The majority of patients underwent a major liver resection. There was no difference in median blood loss, R0 resection rate, morbidity or mortality between groups. There was one post-operative death in the non-PCI group, 4 weeks after surgery, as a result of pneumonia. The only significant difference between the groups was that more patients in the PCI group required a two-staged liver resection [$n = 7$ (8%)] compared with the non-PCI group [$n = 2$ (1%), $P = 0.029$].

Disease recurrence

The sites of intra-hepatic recurrence are shown in Table 6. There was no difference in the recurrence rates at the surgical margin but significantly more patients in the non-PCI group developed intra-hepatic recurrence at new sites (65% vs. 48%, $P = 0.041$). More patients in the PCI group developed recurrence at sites of disappearing metastases compared with the non-PCI group (16% vs. 3%, $P = 0.005$).

The rate of intra-hepatic recurrence over time is shown in Fig. 2. While patients in the PCI group had a lower recurrence rate compared with those in the non-PCI group, this failed to reach statistical significance ($P = 0.1$, log rank test). When the rate of intra-hepatic recurrence was analysed according to the radiological response to chemotherapy, a significant risk stratification was observed. Patients with the same number of CRLM pre- and post-chemotherapy had a significantly reduced risk of liver recurrence compared with those patients whose had at least one lesion disappear with chemotherapy (HR 1.51, $P = 0.014$) or those patients who developed additional CRLM on the post-chemotherapy MRI scan (Hazard ratio 2.03, $P = 0.007$) (Fig. 3). A sub-group analysis within each group demonstrated similar stratification of outcomes (Fig. 4a–b). When only those patients with the same number of CRLM pre- and post-chemotherapy are analysed, a significant increase in intra-hepatic recurrence is seen for patients in the non-PCI group [HR = 2.02, 95% confidence interval (CI) 1.10–3.73, $P = 0.024$] (Fig. 5).

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Table 2 Patient demographics and tumour characteristics

Variable	Total (range or %)	PCI group (range or %)	Non-PCI group (range or %)	*P*-value
Gender				
Male	160 (66)	61 (66)	99 (66)	1.0**
Female	82 (34)	31 (34)	51 (34)	
Age (median years)	63 (30–85)	63 (30–79)	63 (30–85)	0.327*
Primary tumour				
Node positive	172 (71)	62 (67)	110 (73)	0.084**
Missing data	5 (2)	3 (3)	2 (1)	
CEA median	4 (0–1679)	4 (0.5–820)	4 (0–1679)	0.890*
CRLM				
Time from diagnosis of primary				
<3 months	183 (75)	67 (73)	116 (77)	0.067**
3 to 12 months	16 (7)	3 (3)	13 (9)	0.100***
>12 months	43 (18)	22 (24)	21 (14)	0.033**
CRLM number				
Pre-chemo median	2 (1–20)	3 (1–14)	2 (1–20)	0.033*
Post-chemo median	2 (0–14)	2 (0–14)	2 (0–14)	0.208*
≤3	171 (71)	57 (62)	114 (75)	0.019**
Size of the largest CRLM				
Pre-chemo median (mm)	30 (4–200)	33 (5–200)	30 (4–130)	0.545*
Post-chemo median (mm)	23 (0–120)	23(0–120)	21 (0–120)	0.302*
<50 mm	182 (75)	71 (77)	111 (74)	0.577**
50 mm or more	60 (25)	21 (23)	39 (26)	
EHD at time of diagnosis	38 (16)	14 (15)	24 (16)	0.862**

*Mann-Whitney *U* test; **Pearson's chi-square test and *** Fisher's exact test.
CEA, carcinoembryonic antigen; CRLM, colorectal liver metastases; EHD, extra hepatic disease.

Table 3 Pre-chemotherapy referral radiology

Referring imaging modality	PCI *n* = 92	Non-PCI *n* = 150
Liver ultrasound	2	0
CT with i.v. contrast	89 (84 available for comparison)	149
Liver-specific MRI		
Poor quality	2	31
Good quality	20	0

PCI, pre-chemotherapy imaging; CT, computed tomography; i.v., intravenous; MRI, magnetic resonance imaging.

Clinical impact of recurrent disease

Forty-eight patients underwent 54 repeat liver resections with an additional 12 episodes of CRLM ablation (either radiofrequency or microwave) for recurrent disease. One other patient underwent an attempted repeat liver resection (included in the 12 patients in the PCI group on an intention-to-treat basis). Significantly more patients in the non-PCI group required at least one repeat liver resection (n = 37/150, 24.7%) compared with those in the PCI group (n = 12/92, 13%, P = 0.034). Two patients out of the 48 (both in the non-PCI group) died within 90 days of their repeat liver resection (3.7% mortality). One patient died of a post-operative myocardial infarction on the first day after his fourth liver resection, 41 months after his first liver resection and the other patient died of a pulmonary embolus 82 days after her second liver resection, 19 months after her first. Significant but non-life-threatening morbidity was seen in a further 11 (22%) patients.

Survival

To date, 64 patients remain recurrence free. In addition, 38 patients are disease free after at least one re-resection and/or ablation. Thus, 102 out of 242 patients (42%) are disease free to date. The median (95% CI) survival for the entire cohort was 42.1 (31.6–52.3) months. There was no statistical difference between the two groups for survival (Fig. 6). However, when overall survival for the entire patient cohort was analysed by response to chemotherapy, the patients who had lesions, which disappeared, did significantly better than either those patients in whom the numbers of metastases remained unchanged, or those patients who developed additional metastases after chemotherapy (median survival 57.7 vs. 50.3 vs. 28.0 months, respectively,

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Table 4 Chemotherapy details

	Total *n* (%)	PCI *n* (%)	Non-PCI *n* (%)	*P*-value
Chemotherapy				
Indication				
Down staging	85 (35%)	37 (40%)	48 (32%)	0.231**
Neoadjuvant	157 (65%)	55 (60%)	102 (68%)	
Agent				
Oxaliplatin based	219 (90%)	85 (92%)	134 (89%)	0.431**
Irinotecan based	23 (10%)	7 (8%)	16 (11%)	
Monoclonal antibodies	31 (17%)	15 (16%)	16 (11%)	
Median (range) no of cycles	6 (3–24)	6 (3–12)	6 (3–24)	0.006*
No. of patients receiving 3–4 cycles	62 (26%)	34 (37%)	28 (19%)	0.003**
Change in no of CRLM after chemotherapy				
No change	137 (57%)	56 (61%)	81 (54%)	0.350**
Increase	35 (14%)	8 (9%)	27 (18%)	0.059**
Decrease	70 (29%)	28 (30%)	42 (28%)	0.770**

*Mann–Whitney *U*-test; **Pearson's chi-square test.
CRLM, colorectal liver metastases.

Table 5 Liver surgery and post-operative course

Variable	Total *n* (%)	PCI *n* (%)	Non-PCI *n* (%)	*P*-value
Surgery				
Major resection	159 (66)	62 (67)	97 (65)	0.639**
Minor resection	83 (34)	30 (33)	53 (35)	
Median (range) blood loss/mL	350 (30–5344)	380 (40–1950)	358 (30–5344)	0.511*
Mortality (90 days)	1 (0.4)	0	1 (0.6)	–
Morbidity	61 (25)	18 (20)	43 (29)	0.787**
Minor	54 (22)	17 (18)	37 (25)	0.261**
Major	7 (3)	1 (2)	6 (4)	0.257***
Resection margin				
Involved	33 (14)	14 (15)	19 (13)	0.571**
<1 mm	24 (9)	10 (11)	14 (9)	0.823**
1–4 mm	62 (26)	25 (27)	37 (25)	0.648**
5–9 mm	44 (18)	16 (18)	28 (19)	0.806**
>10 mm	75 (31)	26 (28)	49 (32)	0.571**
No lesion seen at pathology	4 (2)	1 (1)	3 (2)	–

*Mann-Whitney *U*-test; **Pearson's chi-square test; ***Fisher's exact test.

$P < 0.001$). This last group with progressive disease on chemotherapy had the worst prognosis (HR = 2.35, 95% CI 1.48–3.71, $P = 0.001$) (Fig. 7).

Discussion

The present study underlines the importance of obtaining a detailed liver-specific MRI scan before the commencement of chemotherapy. Not only did a detailed MRI change the intra-hepatic staging in 56% of patients with CRLM, it was associated with a reduced incidence of new lesions within the liver after hepatic resection. Patients denied such detailed pre-chemotherapy imaging underwent a higher number of repeat liver resections to achieve a similar long-term outcome. Repeat liver resections for recurrent CRLM are more technically challenging and submit the patient to additional mortality and morbidity.[24,25] A detailed liver-specific MRI before chemotherapy could avoid this.

The logical explanation for these results is that lesions that would have been detected by a liver-specific MRI had undergone a complete radiological response (CRR) during the neoadjuvant chemotherapy and were therefore not detected on the subsequent pre-operative MRI. Any lesion outside the planned resection has a

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Table 6 Site of any intra-hepatic recurrence

Site of liver recurrence	PCI *n* (%)	Non PCI *n* (%)	*P*-value
Surgical margin	13 (30)	23 (23)	0.371*
New site	21 (48)	63 (65)	0.041*
Site of disappearing metastasis not resected	7 (16)	3 (3)	0.005**
Unknown	3 (6)	8 (9)	1**

*Pearson's-chi square test; **Fisher's exact test.
PCI, pre-chemotherapy imaging.

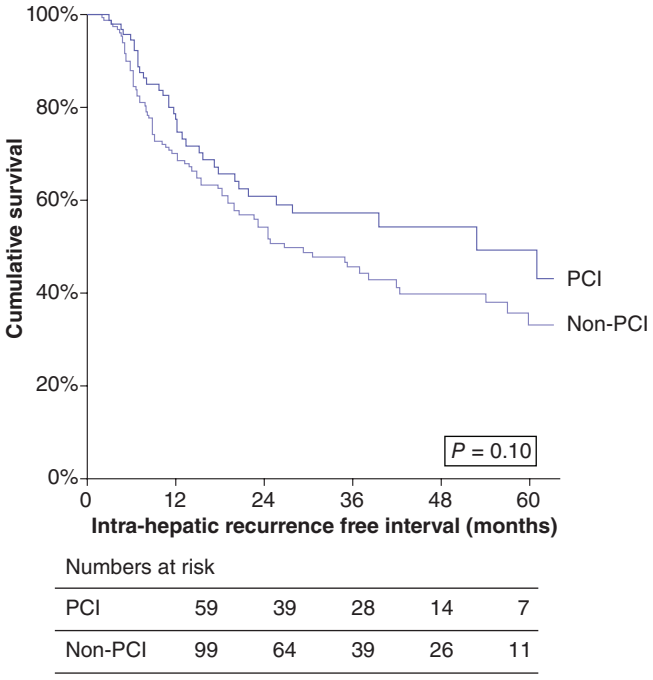

Figure 2 Kaplan–Meier plot to show intra-hepatic recurrence-free survival in the pre-chemotherapy imaging (PCI) and non-PCI groups

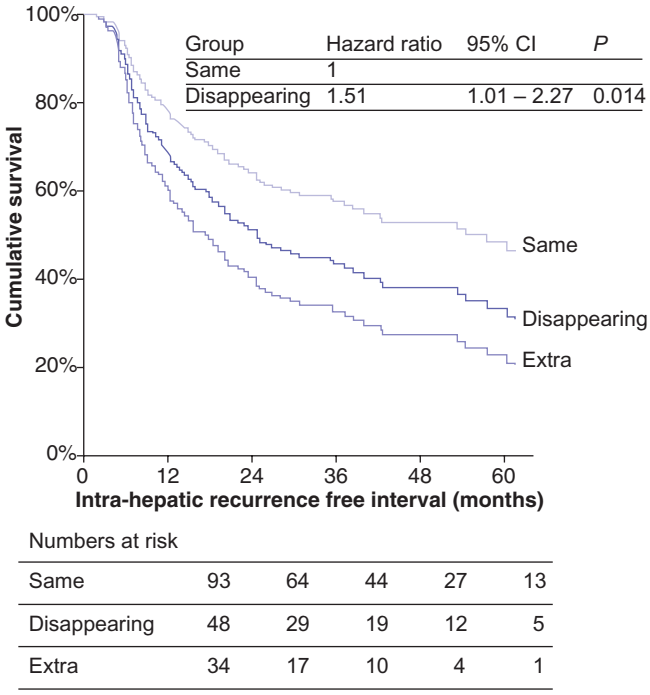

Figure 3 Kaplan–Meier plot to show intra-hepatic recurrence-free survival according to number of colorectal liver metastases (CRLM) before and after chemotherapy

high chance of being undetected at the time of surgery (even by intra-operative ultrasound) and left *in situ*, predisposing to an early liver recurrence.[12,26,27]

Predictors of a patient with CRLM having at least one metastasis that disappears include small size of CRLM (<3 cm), a partial or complete response to chemotherapy,[12] multiple (>3) CRLM and longer duration of chemotherapy.[27] In the present study, the median size of additional CRLM detected by MRI was 8 mm (range 4–30 mm), and over two-thirds of patients had a significant response to chemotherapy. This is at the upper end of reported response rates for neoadjuvant CRLM chemotherapy[28] and reflects the inclusion of only oxaliplatin or irinotecan-based regimes, with at least three cycles successfully delivered. Given the high response rate and small size of additional CRLM seen on the pre-chemotherapy liver MRI, it is likely many patients in the inadequately-imaged group would have come to surgery with unrecognized metastases. The crucial question becomes whether knowledge of these sites alters disease outcome.

When time to liver recurrence is plotted on a Kaplan–Meier curve, a stable observable difference in hepatic recurrence-free survival is seen, but significance is not reached ($P = 0.100$) (Fig. 2). However, a significant stratification of recurrence risk is seen when the change in number of CRLM during chemotherapy is analysed (Fig. 3). Those with the same number of CRLM pre- and post-chemotherapy have the least risk of liver recurrence compared with those with fewer or extra lesions. Patients with extra metastases in the adequately imaged group will by definition have progressive disease[19] and be at a greater risk of early intrahepatic recurrence.[29] For the inadequately imaged group, additional lesions seen on the post-chemotherapy MRI will have either progressive disease or metastases missed on the initial imaging which are now seen on the liver-specific MRI. This group does contain more patients with extra metastases after chemotherapy, but this just fails to reach significance (18% vs. 9%; $P = 0.059$).

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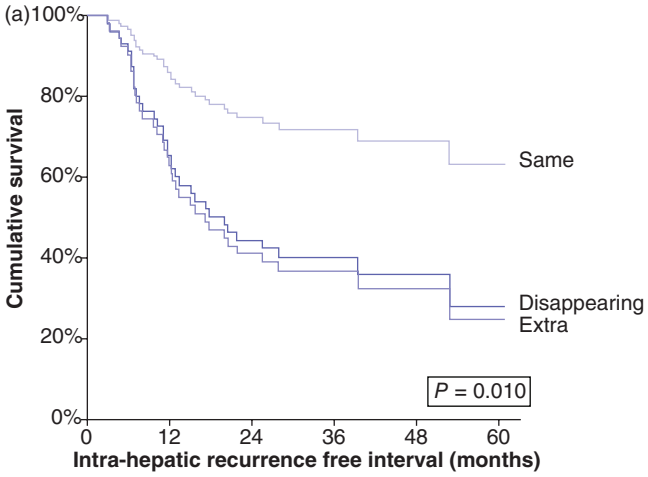
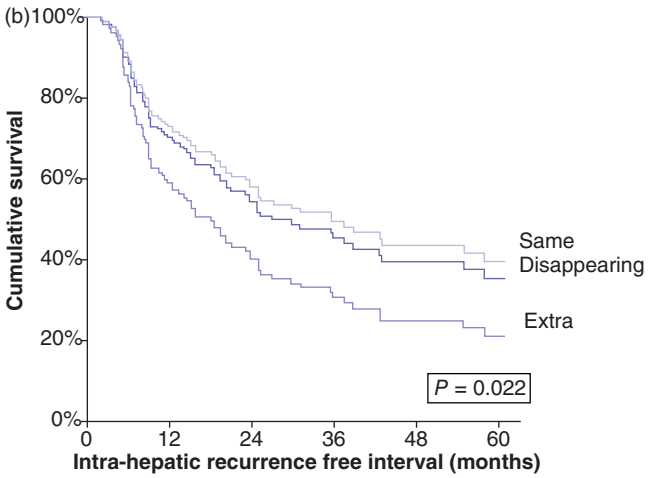
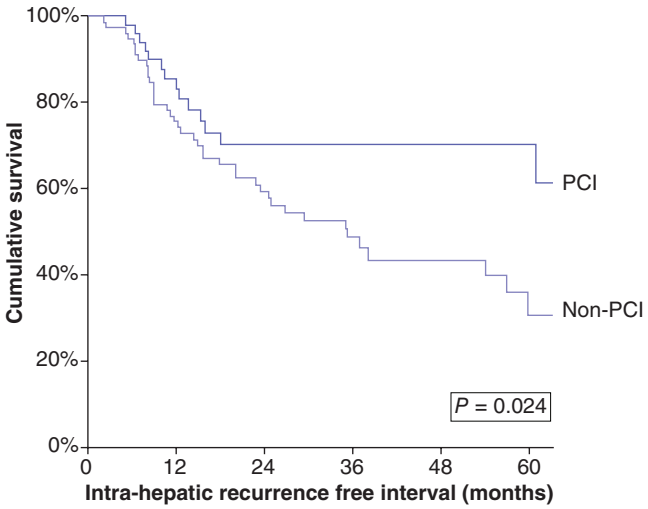


Numbers at risk					
Same	36	25	19	12	7
Disappearing	19	11	7	2	1
Extra	5	4	3	2	1



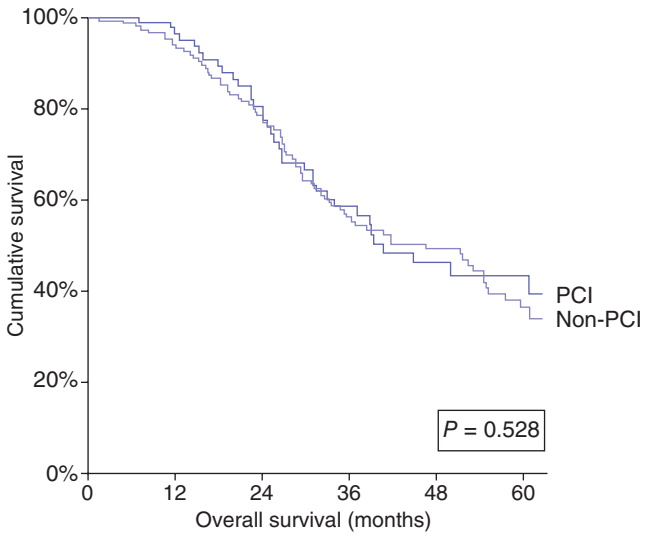
Numbers at risk					
Same	58	39	25	15	6
Disappearing	29	18	12	10	4
Extra	13	7	3	2	1

Figure 4 (a) Kaplan–Meier plot to show intra-hepatic recurrence-free survival according to number of colorectal liver metastases (CRLM) before and after chemotherapy in the pre-chemotherapy imaging (PCI) group. (b) Kaplan–Meier plot to show intra-hepatic recurrence-free survival according to number of CRLM before and after chemotherapy for the non-PCI group



Numbers at risk					
PCI	36	25	19	12	8
Non-PCI	57	39	25	15	6

Figure 5 Kaplan–Meier plot to show the intra-hepatic recurrence-free survival in patients with same number of colorectal liver metastases (CRLM) pre- and post-chemotherapy according to patient groups [pre-chemotherapy imaging (PCI) and non-PCI)



Numbers at risk					
PCI	77	54	36	19	12
Non-PCI	138	103	67	46	24

Figure 6 Kaplan–Meier survival plot of overall survival for pre-chemotherapy imaging (PCI) and non-PCI groups

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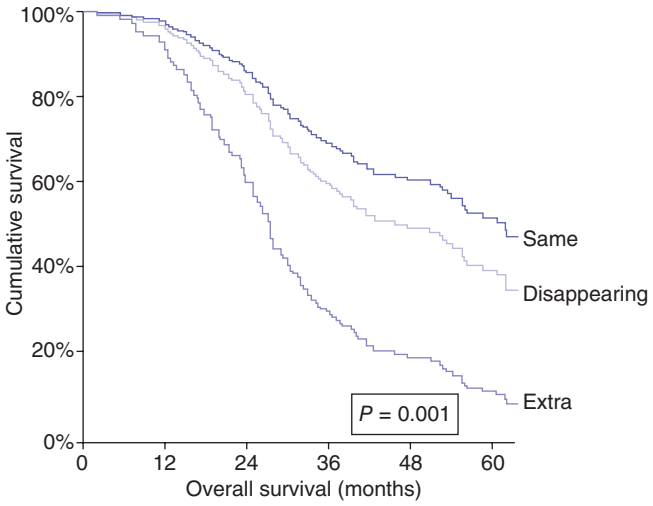

Numbers at risk

Same	118	90	63	39	22
Disappearing	59	48	31	23	13
Extra	33	30	19	9	3

Figure 7 Kaplan–Meier plot shows overall survival for the entire cohort according to the radiological response to chemotherapy

Those with known disappearing lesions during chemotherapy are expected to have a favourable overall outcome after CRLM resection, as they are chemo-responsive.[28] However, the rate of liver recurrence in these patients is higher than in those with the same number of metastases. It is our philosophy to try to resect all original sites of metastatic disease. However, a metastasis that is no longer detectable on MRI or intra-operatively will often require a localized segmental or wedge resection that is difficult to perform without endangering key hepatic vascular or biliary structures. Furthermore, a blind resection cannot guarantee a clear margin and on occasion we have left such lesions *in situ* and followed them closely with serial imaging, aiming for a repeat resection if and when they recur. This may explain why, despite the favourable response to chemotherapy, the patients with disappearing lesions have a higher rate of liver recurrence (HR = 1.51 95% CI 1.1–2.27, $P = 0.014$) than those with the same number. Van Vledder and colleagues similarly demonstrated that patients with unresected metastases that disappeared have higher rates of intrahepatic recurrence.[27]

The present findings give further indirect evidence that metastases that disappear with chemotherapy do recur and that every effort should be made to identify and resect them. Benoist and co-workers[12] reported the recurrence of CRLM at the site of unresected disappearing lesions in 23 of 31 (74%) lesions after 1 year of follow-up. Tanaka and co-workers[26] reported similar findings, with *in situ* recurrence of lesions which disappeared, in 11 of 27 (41%) lesions, at a median of 14 months follow-up. Both series identified a residual tumour in 60–80% of patients that were resected. Other workers have found a better correlation of complete radiological response (CRR) with a complete pathological response (CPR) but still report recurrence in 27–38% of patients.[30]

An argument in favour of administering chemotherapy before liver resection is that this allows an assessment of the tumour biology. Rather than the radiological response to chemotherapy, the pathological response is emerging as the most accurate and important prognostic indicator.[31] Several authors have found a strong correlation with the degree of pathological response and outcome.[26,31,32] Those with a CPR have the best outcomes and yet a CRR only poorly correlates with a CPR. As many lesions that have undergone a CPR are still visible on imaging and residual viable tumour can be found in 60% to 80% of lesions which have a CRR that are resected.[12,26] In our cohort, 11 out of 242 patients (4.5%) had a CPR in all lesions on histology. Yet only one of these had a CRR during chemotherapy. Similarly, Tanaka *et al.* found 58% of lesions with CPR occurred in CRLM still seen on a pre-operative CT imaging[26] and concluded that no modern imaging technique, even PET-CT, can reliably predict CPR and therefore, assessment of CPR ultimately depends on histopathological examination. It appears that the pathological response occurs early in systemic treatment. Ribero and colleagues, using a regimen of 5FU, Oxaliplatin (FOLFOX) and Bevacizumab, showed that only two to four cycles is required for CPR and that the addition of more chemotherapy had no additional response.[33] In contrast, CRLM are more likely to exhibit a radiological response and disappear with longer durations of chemotherapy.[27] Our patients received a median number of 6 (range, 3–24) cycles of chemotherapy before surgery. This was in spite of the majority (65%) receiving their chemotherapy in the setting of known resectable CRLM. Interestingly, those with more detailed imaging were more likely to receive only three to four cycles of pre-operative chemotherapy. These patients were often referred before starting their systemic treatment and it is possible that referral to a hepatobiliary surgeon results in a lesser amount of pre-operative chemotherapy or certainly earlier re-staging because of concerns regarding hepatoxicity and disappearing lesions. In addition, there is a group of patients in whom the CRLM remains just visible on the pre-operative MRI but are not seen or palpable at the time of surgery owing to severe steatosis and small size. These patients are as difficult to manage. While some have advocated the placement of radiological placed coils next to lesions at risk of disappearing,[34] we worry about the associated morbidity and theoretical risk of tumour seeding.[35] Thus we advocate limiting preoperative chemotherapy to the two to four cycles needed to elicit a pathological response before performing surgery in the case of resectable CRLM, or re-staging in the case of conversion chemotherapy. It may be preferable to avoid pre-operative chemotherapy altogether, in the cases of small isolated CRLM (<3 cm).

While the strength of the present study is the large number of patients undergoing a potent, modern chemotherapy regime with radiological and clinical outcomes collected on a robust

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prospective database, the study design is still retrospective and has several limitations. First, this is a selected population containing only 34% (242 of 715) of all patients undergoing a liver resection for CRLM at our institution over the study period. In all, 41% did not receive any pre-operative chemotherapy and another 37% received what we have called a sub optimal pre-operative chemotherapy regime. Not surprisingly our cohort therefore contains a high incidence of CRLM that disappear during treatment that would lend itself to the study's hypotheses. But as pre-operative chemotherapy becomes increasingly used and Oxaliplatin- and Irinotecan-based regimes are now the standard of care in the first-line systemic treatment of CRLM[36] we feel this makes the present study population, and the outcomes, increasingly pertinent.

We also acknowledge that this is not a formal diagnostic comparison of imaging modalities. This was never the aim of the present study as we set out to study the clinical outcome of omitting a detailed pre-chemotherapy MRI scan. What is clear is that a detailed liver MRI alters the liver staging of over half the patients before chemotherapy is started. Finally the retrospective design has meant that it was not possible to accurately identify how many known CRLM that disappeared were able to be detected at the time of surgery nor to accurately identify all patients who had such lesions left *in situ*.

Conclusion

We have shown that a detailed high-quality MRI assessment of CRLM before pre-operative chemotherapy changed the intrahepatic lesion detection in 56% of patients. Patients denied adequate pre-chemotherapy radiological staging underwent a significantly higher re-intervention with surgery and/or ablation to achieve a similar outcome. We would urge all Oncologists to obtain a liver-specific MRI where possible before starting chemotherapy.

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