Original article

Outcomes after resection and/or radiofrequency ablation for recurrence after treatment of colorectal liver metastases

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Background: **Repeat liver resection for colorectal liver metastases (CRLMs) is possible in a limited number of patients, with radiofrequency ablation (RFA) as an alternative for unresectable CRLMs. The aim of this study was to analyse survival rates with these interventions.**

Methods: **This was a database analysis of patients who underwent first and repeat interventions for synchronous and metachronous CRLMs between 2000 and 2013. Descriptive and survival statistics were calculated.**

Results: **Among 431 patients who underwent resection or RFA for CRLMs, 305 patients developed recurrences for which 160 repeat interventions (resection and/or RFA or ablative radiotherapy) were performed. In total, after 707 first or repeat interventions, 516 recurrences (73·0 per cent) developed, of which 276 were retreated curatively. At the time of first intervention, independent risk factors for death were lymph node-positive primary tumour (hazard ratio (HR) 1·40; $P = 0·030$), more than one CRLM (HR 1·53; $P = 0·007$), carcinoembryonic antigen level exceeding 200 ng/ml (HR 1·89; $P = 0·020$) and size of largest CRLM greater than 5 cm (HR 1·54; $P = 0·014$). The 5-year overall survival rates for liver resection and percutaneous RFA as first intervention were 51·9 and 53 per cent, with a median overall survival of 65·0 (95 per cent c.i. 47·3 to 82·6) and 62·1 (52·2 to 72·1) months, respectively.**

Conclusion: **RFA had good oncological outcomes in patients with unresectable CRLMs. Radiofrequency ablation is progressively more applied with each additional intervention.**

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Introduction

Liver resection is a potentially curative treatment for patients with colorectal liver metastases (CRLMs), with 5-year survival rates of 30–50 per cent[1]. Both large single-centre studies and systematic reviews have provided evidence that repeat hepatectomy is feasible in selected patients with intrahepatic recurrences[1–7]. Despite this, repeat hepatectomy may not be possible owing to anatomical or functional restraints[8,9]. Radiofrequency ablation (RFA) is a useful alternative in this situation. The aim of this study was to analyse outcomes following repeat interventions for hepatic or extrahepatic recurrences after initial liver surgery.

Methods

The hepatopancreatobiliary unit of University Medical Centre Groningen is a secondary and tertiary referral centre for patients with CRLMs in the north-eastern part of the Netherlands. This study was approved by the local medical ethics committee (METc2015/343). It comprised an analysis of a database of patients who underwent first and repeat interventions for synchronous and metachronous CRLMs between 2000 and 2013. August 2013 was chosen as the last inclusion time point to achieve a minimum follow-up of 1 year. Patients who underwent a two-stage intervention, such as liver first followed by treatment of synchronous pulmonary metastases, were included. Liver-directed treatments were liver resection and/or open RFA or percutaneous RFA. RFA was performed

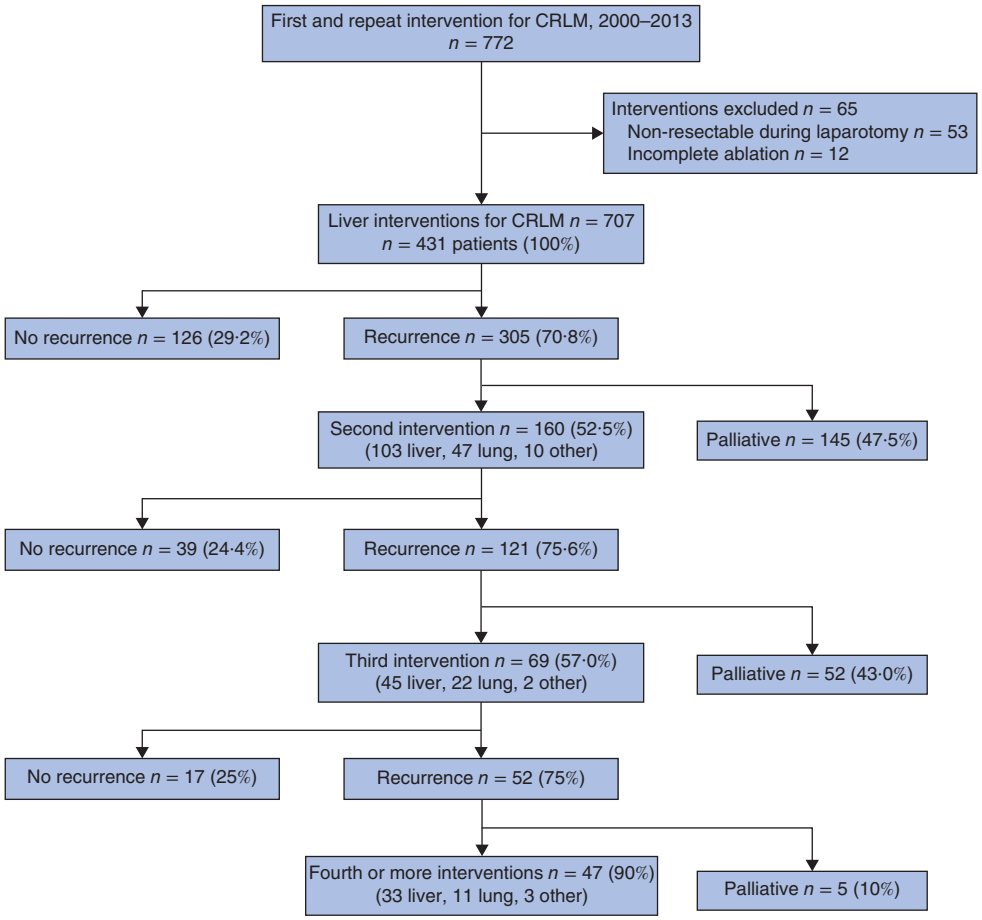


Fig. 1 Overview of selection of patients and their distribution over the first four interventions. Recurrences, irrespective of site, became apparent 516 times after 707 interventions (73·0 per cent). A repeat intervention was possible in 276 (53·5 per cent) of these 516. First and later liver-only recurrences occurred in 188 patients, of whom 151 (80·3 per cent) underwent a repeat intervention with curative intent. CRLM, colorectal liver metastasis

using an RF3000^{TM} Radiofrequency Ablation System (Boston Scientific, Marlborough, Massachusetts, USA) according to the manufacturer's instructions. Depending on the size of the metastasis, LeVeen electrodes with a diameter of 2·0, 3·5, 4·0 or 5·0 cm were applied. Open RFA was performed using ultrasound guidance in patients who had a laparotomy for simultaneous interventions. In general, RFA was contraindicated for CRLMs with a diameter exceeding 5 cm.

Follow-up consisted of a 3-monthly survey in the first 2 years after surgery, and every 6 months thereafter, including serum carcinoembryonic antigen (CEA) level, ultrasound examination of the liver and chest X-ray or, if indeterminate, multiphase enhanced CT[10]. If this was still indeterminate, MRI was carried out. CT–PET with fluorodeoxyglucose was performed when the results of CT or MRI were equivocal. Each patient was discussed in a multidisciplinary team meeting.

RFA was carried out according to standard terminology[11,12]. If ablation was considered incomplete on CT at 1 week after ablation, one or more additional sessions (so-called 'completion ablations' to obtain 'technical success') were performed immediately. Follow-up imaging of RFA-treated patients was done by CT.

The number of CRLMs and the size of the largest lesion were based on pathological findings in resection specimens, and on CT or MRI images in patients treated with RFA. The date of the (repeat) intervention was the starting point for the survival analysis. This means that, for repeat interventions, the time lapse for the development and detection of recurrences after the initial treatment was eliminated.

Table 1 Clinicopathological characteristics of all patients at time of first liver intervention

	Total ($n = 431$)	Liver resection ($n = 261$)	Open RFA ($n = 26$)	Percutaneous RFA ($n = 75$)	Resection + RFA ($n = 69$)	P‡
Patient characteristics						
Age (years)*	62·9(9·4)	63·4(8·9)	60·2(10·8)	65·7(8·5)	59·3(10·4)§	
Sex ratio (M : F)	264 : 167	151 : 110	14 : 12	55 : 20	44 : 25	
Preoperative factors						
Neoadjuvant chemotherapy	138 (32·0)	55 (21·1)	7 (31)	32 (43)	44 (64)	< 0·001
Low CRS (0–2)	285 (66·1)	179 (68·6)	18 (69)	54 (72)	34 (49)	0·018
Synchronous CRLMs	201 (46·6)	107 (41·0)	18 (69)	31 (41)	45 (65)	< 0·001
DFI > 12 months	137 (31·8)	96 (36·8)	4 (15)	23 (31)	14 (20)	0·020
CEA > 200 ng/ml	26 (6·0)	20 (7·7)	0 (0)	2 (3)	4 (6)	
Characteristics of primary tumour						
Rectal site	196 (45·5)	115 (44·1)	13 (50)	34 (45)	34 (49)	
Node-positive disease	261 (60·6)	155 (59·4)	17 (65)	50 (67)	39 (57)	
Characteristics of CRLMs						
Diameter (cm)†	3·5 (2·0–5·0)	4·0 (2·5–5·7)¶	2·2 (1·4–3·0)	2·2 (1·5–3·5)	3·0 (2·0–4·4)	
> 1 CRLM	210 (48·7)	100 (38·3)	12 (46)	29 (39)	69 (100)	< 0·001
Type of resection ($n = 330$)						< 0·001
(Extended) hemihepatectomy	183 (55·5)	160 (61·3)	–	–	23 (33)	
(Bi)segmentectomy	70 (21·2)	45 (17·2)	–	–	25 (36)	
Wedge resection	77 (23·3)	56 (21·5)	–	–	21 (30)	

Values in parentheses are percentages unless indicated otherwise; values are *mean(s.d.) and †median (i.q.r.). RFA, radiofrquency ablation; CRS, clinical risk score; DFI, disease-free interval between primary tumour treatment and detection of colorectal liver metastases (CRLMs); CEA, carcinoembryonic antigen. ‡χ^2 test between groups; §$P = 0{\cdot}007$ *versus* liver resection and $P = 0{\cdot}001$ *versus* percutaneous RFA (Student's t test); ¶$P \leq 0{\cdot}001$ *versus* open RFA, percutaneous RFA and resection + RFA (Mann–Whitney U test).

Statistical analysis

Summary statistics are presented as percentages, median (i.q.r.) or mean(s.d.), with analysis by χ^2 test, Mann–Whitney U test and Student's t test, as appropriate. Survival rates were estimated by the Kaplan–Meier method, with comparisons made using the log rank test. Patients with an uncertain recurrence status (such as postoperative mortality in hospital) were excluded from analysis of recurrences. Median survival rates and 95 per cent confidence intervals (c.i.) were noted, as well as 5-year survival rates. Factors associated with survival were examined by means of univariable and multivariable Cox regression analyses. Factors with $P \leq 0{\cdot}100$ in univariable analysis were entered into the multivariable model. Hazard ratios and 95 per cent c.i. were calculated and $P < 0{\cdot}050$ was considered significant. Statistical analyses were performed with SPSS® version 22 (IBM, Armonk, New York, USA).

Results

Among 772 interventions, more widespread disease than expected was encountered in 53 exploratory laparotomies, which required cancellation (*Fig. 1*). Ablation was considered incomplete in 12 patients at the 1-week CT scan and a second RFA intervention was performed immediately, but not counted as a separate intervention. *Table 1* shows the clinicopathological characteristics of the 431 patients with potentially curable disease at the time of the first liver intervention. The clinical risk score[13] showed more advanced disease in patients undergoing simultaneous resection and RFA.

Neoadjuvant chemotherapy was administered before 161 (22·8 per cent) of the 707 first and repeat interventions. In 98 (60·9 per cent) of 161 this consisted of capecitabine and oxaliplatin. Two or three cycles of neoadjuvant chemotherapy were given, after which the response was evaluated by contrast-enhanced CT. If CT indicated that an R0 procedure could be performed, no further cycles were administered; otherwise two or three additional cycles were given. *Fig. 1* shows the selection of patients, and the distribution of patients undergoing curative and palliative treatments at each subsequent intervention. *Fig. 2* and *Table S1* (supporting information) show the types of procedure carried out at each intervention. Thirty-two portal vein embolizations were performed in combination with an intervention. Six two-stage liver resections were done. No associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) procedures were performed.

Median follow-up was 38·6 (i.q.r. 19·5–61·7) months. At the end of follow-up, 212 (49·2 per cent) of the 431 patients had died, 163 (37·8 per cent) were alive and free from disease, and 56 (13·0 per cent) were alive with recurrent disease. The 30-day mortality rate for all interventions was 0·7 per cent (5 of 707).

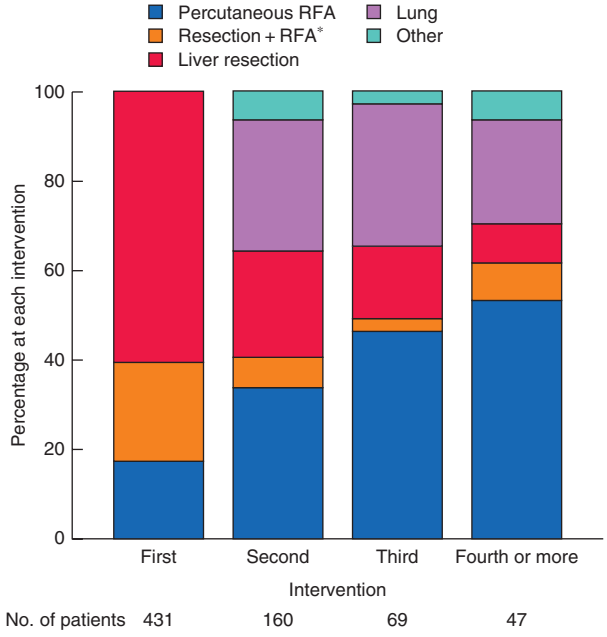


Fig. 2 Distribution of treatments at the first, second, third and fourth or more intervention. *Includes open radiofrequency ablation (RFA)

Predictors of survival

Median overall survival of the total study population was 55·6 (95 per cent c.i. 47·0 to 64·1) months and median disease-free survival was 45·5 (40·2 to 50·8) months. Five-year overall survival was 47·8 per cent and disease-free survival was 40·7 per cent. On multivariable analysis of variables at the time of the first intervention, node-positive primary tumour, more than one CRLM, CEA level exceeding 200 ng/ml and size of largest CRLM greater than 5 cm were associated with overall survival. Of note, these factors are all included in the clinical risk score (*Table 2*).

First *versus* repeat interventions

Fig. 3 shows survival stratified according to the time of the first, second or third and higher intervention. Obviously, measuring survival times from the date of the first intervention resulted in progressively longer survival in patients undergoing a repeat intervention. Survival was lower after the second and third or higher interventions, but the overall 5-year survival rate was still about 25 per cent. There was no difference in survival measured from the first intervention between patients who underwent one intervention compared with those who had two interventions or those who underwent three or more interventions ($P = 0{\cdot}212$) (*Fig. 4a*). *Fig. 4b* shows survival from the last intervention.

The risk of recurrence after the first intervention for CRLMs was 70·8 per cent (305 of 431). The recurrence rate was independent of the number of interventions ($P = 0{\cdot}745$). The median size of treatable recurrent CRLMs was 2·7 (i.q.r. 1·9–3·5) cm, smaller than that of

Table 2 Prognostic factors associated with overall survival identified by univariable and multivariable Cox regression analysis at the time of the first intervention in patients who had first and repeat interventions

	Univariable analysis		Multivariable analysis	
	Hazard ratio	*P*	Hazard ratio	*P*
Patient factors				
Age > 60 years	1·09 (0·83, 1·44)	0·539	–	–
Male sex	0·89 (0·67, 1·17)	0·397	–	–
Clinical risk score				
Node-positive disease	1·37 (1·03, 1·82)	0·033	1·40 (1·03, 1·90)	0·030
DFI < 12 months	1·24 (0·92, 1·66)	0·158	–	–
> 1 CRLM	1·58 (1·20, 2·07)	0·002	1·53 (1·12, 2·09)	0·007
CEA > 200 ng/ml	2·20 (1·36, 3·60)	0·001	1·89 (1·11, 3·22)	0·020
Size of CRLM > 5 cm	1·57 (1·17, 2·10)	0·001	1·54 (1·09, 2·17)	0·014
Primary tumour				
Rectal location	1·01 (0·77, 1·34)	0·923	–	–
Synchronous CRLMs	0·92 (0·70, 1·21)	0·549	–	–
Treatment				
Neoadjuvant chemotherapy	1·28 (0·95, 1·71)	0·100	1·07 (0·76, 1·52)	0·685
Liver resection only	0·78 (0·59, 1·04)	0·087	0·74 (0·54, 1·03)	0·071
Percutaneous RFA	0·91 (0·60, 1·35)	0·651	–	–
> 1 intervention	1·19 (0·90, 1·58)	0·226	–	–

Values in parentheses are 95 per cent confidence intervals. DFI, disease-free interval between primary tumour treatment and detection of colorectal liver metastases (CRLMs); CEA, carcinoembryonic antigen.

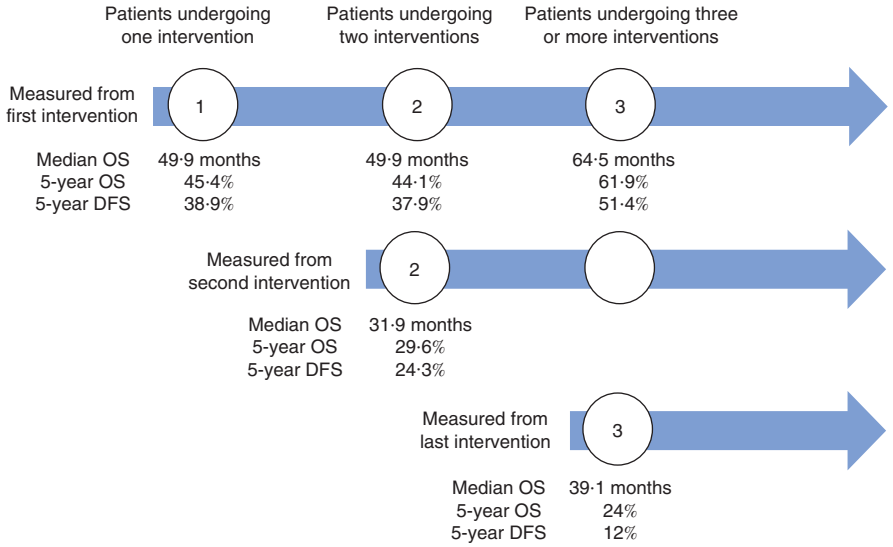
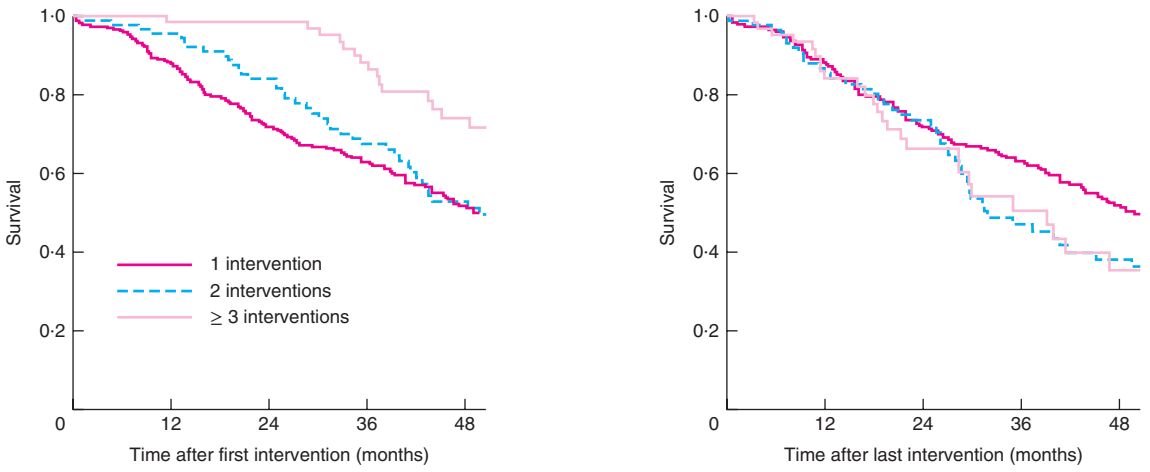


Fig. 3 Survival of patients undergoing one, two and three or more interventions measured from the date of the first, second and last intervention. OS, overall survival; DFS, disease-free survival



No. at risk

1 intervention	270	230	162	131	94
2 interventions	91	87	70	50	32
≥ 3 interventions	69	68	64	50	31

a Overall survival after first intervention

No. at risk

1 intervention	270	230	162	131	94
2 interventions	90	65	52	27	21
≥ 3 interventions	69	44	27	14	8

b Overall survival after last intervention

Fig. 4 Kapan–Meier overall survival curves measured from **a** date of first intervention and **b** date of last intervention for patients who had one, two, or three or more interventions. **a** $P = 0{\cdot}212$, **b** $P = 0{\cdot}043$ (log rank test)

the initial metastases, which measured 3·5 (2·0–5·0) cm. The 5-year survival rate for patients who had palliative treatment was 13·1 per cent measured from the first intervention and 7·0 per cent measured from the discovery of recurrence, with median overall survival of 31·0 (95 per cent c.i. 23·5 to 38·6) and 18·0 (14·7 to 21·3) months respectively.

Liver resection *versus* percutaneous radiofrequency ablation

At the start of RFA treatment in 2000, RFA was performed only when liver resection was not possible technically, or a sole treatment was not able to render the liver tumour-free. Interim analysis of RFA showed favourable results, leading to a more liberal indication for this procedure in more

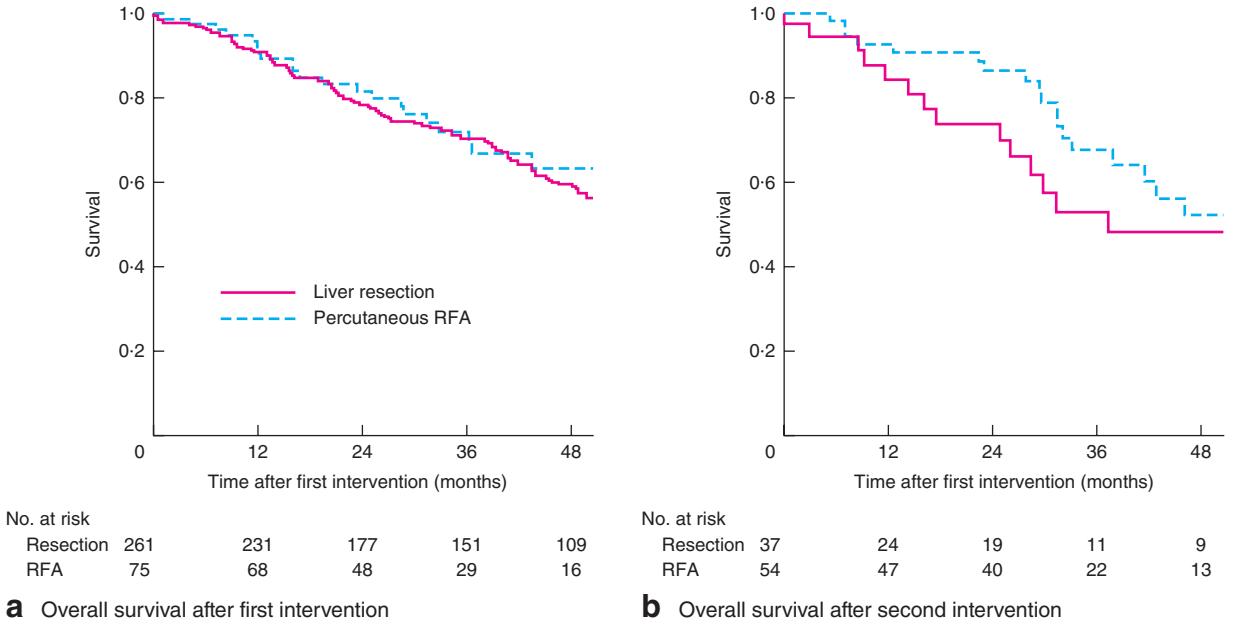


Fig. 5 Kapan–Meier overall survival curves **a** after liver resection *versus* percutaneous radiofrequency ablation (RFA) as first intervention and **b** after liver resection *versus* first percutaneous RFA as second intervention for first recurrence of metastatic colorectal cancer. **a** $P = 0{\cdot}979$, **b** $P = 0{\cdot}704$ (log rank test)

recent years. A liver resection was technically possible in 54 (29·0 per cent) of 186 patients who underwent percutaneous RFA, but was precluded by co-morbidity or patient choice. The overall recurrence rate was 83·5 per cent (152 of 182) following percutaneous RFA compared with 66·6 per cent (201 of 302) for liver resection ($P < 0{\cdot}001$). Intrahepatic recurrence rates were 59·9 per cent (91 of 152) in the percutaneous RFA group *versus* 23·9 per cent (48 of 201) in the liver resection group ($P < 0{\cdot}001$). The risk of ablation-site recurrence after percutaneous RFA was 26·9 per cent (50 of 186 patients; 250 lesions treated in total). Ablation-site recurrence could again be treated with curative intent in 46 interventions (92 per cent), and consisted of repeat RFA in 41 and resection in five. Despite a higher recurrence rate after percutaneous RFA compared with liver resection, overall survival was no different (*Fig. 5*). The 5-year overall survival rates for liver resection and percutaneous RFA as first intervention were 51·9 and 53 per cent, with a median overall survival of 65·0 (95 per cent c.i. 47·3 to 82·6) and 62·1 (52·2 to 72·1) months, respectively.

Location of recurrence

The location of recurrences had an impact on survival (*Fig. S1* and *Table S2*, supporting information). Video-assisted thoracoscopic surgery was performed in 45 patients and 34 patients underwent stereotactic body radiation therapy for lung metastases. One patient underwent both lung treatments in one intervention. Recurrences after video-assisted thoracoscopic surgery occurred in 37 of 45 patients (22 of 37 lung-only recurrences), whereas 21 of 34 patients developed recurrences (8 of 21 lung-only) after stereotactic body radiation therapy. Forty-seven patients developed lung metastases after initial liver intervention, of whom 32 underwent video-assisted thoracoscopic surgery and 15 stereotactic body radiation therapy. There was no difference in 5-year overall survival rates of 39 *versus* 42 per cent, and median overall survival of 49·5 (95 per cent c.i. 28·4 to 70·6) *versus* 53·9 (14·4 to 93·3) months, for video-assisted thoracoscopic surgery *versus* stereotactic body radiation therapy ($P = 0{\cdot}500$).

Discussion

The main findings of the present study were that RFA, in particular via the percutaneous route, substantially increased the number of patients who could be treated for recurrent CRLMs. In addition, repeat interventions were possible in more than half of the patients. Even patients who had three or more repeat interventions achieved an overall 5-year survival rate of about 25 per cent.

Several papers[1–7,14,15] have reported repeat interventions in 27–48 per cent of patients with recurrence, compared

with 53·5 per cent here. Treating a second metastatic recurrence has been reported in about half of patients, with a 5-year survival rate of 27 per cent[6].

The reported results of percutaneous RFA for recurrent CRLM are reasonable, and this procedure increases the number of patients who were otherwise untreatable[16–18]. Another advantage of (percutaneous) RFA is a much shorter hospital stay, and lower costs compared with liver resection[19]. The disadvantages of RFA are incomplete ablation and the development of ablation-site recurrence, which can be considered a failure of treatment. However, repeat interventions can be achieved easily, apparently without compromising long-term outcome.

The most common sites of recurrent disease after treatment for CRLM are the liver and lung[20,21]. In one study[22] patients who underwent liver surgery first because of CRLM, and lung metastasectomy at a later date, had similar survival to patients who underwent lung metastasectomy alone. In other words, previous liver surgery does not preclude resection of lung metastases. The present authors and others[15,23,24] have demonstrated that, in patients with treatable recurrences, pulmonary recurrences have the best prognosis.

Limitations of this study include its retrospective design and the gradual change in indications for resection and RFA over the study. This study describes the results of decision-making in daily common practice. This probably led to bias in the treatment groups compared. However, the strategy of using RFA offers a potentially curative treatment to patients who would otherwise be deemed untreatable and condemned to palliative chemotherapy.

Disclosure

The authors declare no conflict of interest.

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Supporting information

Additional supporting information may be found in the online version of this article:

Table S1 Treatments undertaken at each intervention (Word document)

Table S2 Survival according to location of recurrence after first intervention (Word document)

Fig. S1 Kaplan–Meier **a** overall and **b** disease-free survival curves according to location of recurrences after the initial intervention (Word document)