Cardiovasc Intervent Radiol (2019) 42:979–990
https://doi.org/10.1007/s00270-019-02219-4

CLINICAL INVESTIGATION INTERVENTIONAL ONCOLOGY

Transarterial Chemoembolisation of Colorectal Liver Metastases with Irinotecan-Loaded Beads: A Bi-institutional Analysis of 125 Treatments in 53 Patients

An Ngo[1] · Conrad von Stempel[2] · Beniamino Corbo[1] · Steve Bandula[2,3] · Kai Keen Shiu[4] · Jowad Raja[2] · Julian Hague[2] · Jonathan Evans[1] · Nabil Kibrya[1]

Received: 6 October 2018 / Accepted: 2 April 2019 / Published online: 1 May 2019

Abstract

Purpose To retrospectively review outcomes in patients treated for colorectal liver metastases with DEBIRI.

Materials and Methods A retrospective analysis of patients with CRLM treated with DEBIRI was performed between 2008 and 2017 between two tertiary centres. Outcome parameters were overall survival and hepatic progression-free survival, as well as safety. Subgroup analyses were performed to assess the impact on outcomes of hepatic tumour burden at time of treatment, the presence of extrahepatic disease, prior systemic chemotherapy and the prior administration of systemic irinotecan-containing chemotherapy.

Results Fifty-three patients received 125 treatments with DEBIRI over the study period. Median age of patients was 71 (range 41–88). Patients previously received a median of 1 line of chemotherapy (range 1–5). Median number of DEBIRI treatments was 2 (range 1–6). The median survival from first treatment was 14.5 months (range 1–107). Median hepatic progression-free survival was 5 months (0–86.5 months). The presence of extrahepatic disease (seen in 45% of patients) correlated with lower OS. Prolonged OS was seen in patients who received previous ablation and systemic chemotherapy. Technical success rate was found to be 99%. Post-procedural complication rate was 6%.

Conclusion Our findings add to the growing body of literature to support the safety profile of DEBIRI in the treatment of CRLM. Further studies will be necessary to help establish the optimum berth of DEBIRI in the treatment algorithm for colorectal liver metastases.

Keywords Colorectal liver metastases · DEBIRI · TACE · Chemoembolisation · Irinotecan

Introduction

Colorectal cancer (CRC) is the third commonest cancer worldwide [1]. The liver is the primary site of metastatic spread, affecting 60–70% of patients during the course of their disease [2]. The development of colorectal liver metastases (CRLM) may profoundly affect prognosis and, left untreated, is associated with a median survival of 5–10 months [3].

Locoregional therapies have been developed for patients with unresectable liver-dominant or liver-only metastatic colorectal cancer refractory to frontline systemic treatment regimens which may offer effective local disease control.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00270-019-02219-4) contains supplementary material, which is available to authorized users.

✉ An Ngo
an.ngo@nhs.net

[1] Department of Interventional Radiology, Royal Liverpool and Broadgreen University Hospital, Prescot St, Liverpool L7 8XP, UK

[2] Interventional Oncology Service, University College Hospital, 235 Euston Road, London NW1 2BU, UK

[3] Centre for Medical Imaging, University College London, 2nd Floor Charles Bell House, 43-45 Foley Street, London W1W 7TS, UK

[4] Department of Oncology, University College Hospital, 235 Euston Road, London NW1 2BU, UK

Such treatment options include transarterial chemoembolisation (TACE) using either emulsions of ethiodised oil and chemotherapy solution (conventional TACE) or drug-eluting microspheres loaded with a chemotherapy agent (DEB-TACE).

The use of drug-eluting beads loaded with irinotecan (DEBIRI) to treat CRLM was first reported in 2006 by Aliberti et al. [4]. Irinotecan is a topoisomerase inhibitor used to treat metastatic colon and rectal cancers. DEBIRI may provide palliation and disease control in patients with CRLM refractory to systemic chemotherapy [5]. Furthermore, the efficacy of DEBIRI in combination with first-line systemic chemotherapy (FOLFOX) in downstaging non-resectable CRLM to resectability has also been demonstrated [6].

The purpose of this retrospective study is to evaluate the outcomes in patients treated with DEBIRI for CRLM at two centres, assessing overall survival (OS), progression-free survival (PFS) and safety.

Materials and Methods

Patients

A retrospective bi-institutional analysis of all patients with histologically confirmed CRLM treated with DEBIRI between 2008 and 2017 was undertaken. The use of DEBIRI was ratified by the Institutional Review Board of both hospitals. Patients were identified for inclusion in the study through review of departmental case logs. Demographic and clinical data were extracted from paper and electronic medical records. All patients treated with DEBIRI were included in the study regardless of age, status of primary tumour, the presence of extrahepatic disease or levels of pre-treatment.

Within the multidisciplinary team meeting (MDT), DEBIRI is considered in selected patients in whom surgical resection, ablation or systemic chemotherapy was not chosen on either clinical or personal grounds, or where progressive hepatic disease has occurred despite previous resection or locoregional therapy rendering the patient unsuitable for further curative treatment (Fig. 1).

DEBIRI TACE Procedure

All treatments were delivered by one of the four interventional radiologists. The procedure was performed under general anaesthesia at one centre and deep sedation with propofol infusion or in combination with percutaneous paravertebral local anaesthetic nerve blocks (T6-T10) at the second centre. Patients in whom recent bilio-enteric intervention had been performed received prophylactic antibiotics.

A standard TACE technique was employed. The decision to treat from a lobar or segmental artery was taken based upon the tumour distribution in terms of location and number. Where segmental treatment delivery was desired, selective catheterisation was performed using a co-axial technique with a 2.7 Fr microcatheter.

DC beads (Biocompatibles, Farnham, UK) of 70–150 μm (M1) or 100–300 μm (M2) were loaded with irinotecan at 50 mg/ml according to the instructions for use. Under fluoroscopic guidance, a solution of 2 ml of DEBIRI (100 mg irinotecan) mixed with normal saline and non-ionic contrast was injected until either the total volume was injected or near stasis was achieved. The actual dose delivered was recorded.

Treatments were scheduled as per the Lencioni protocol [7]. Follow-up imaging (CT or MRI) was routinely performed at 6 weeks post-procedure, followed by three monthly intervals.

Clinical and Radiological Analyses

The procedure was considered a technical success if the treatment was completed in full as described above. Adverse events were recorded and categorised according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

The hepatic lobe distribution of disease, total tumour load as a percentage of total liver volume and the presence of extrahepatic disease were recorded following review of the pre-treatment diagnostic imaging. Radiological response rate was assessed in accordance with the Response Evaluation Criteria in Solid Tumours (RECIST) criteria (version 1.1) on follow-up imaging.

Statistical Analysis

The Kaplan–Meier method was utilised to estimate survival probabilities and median progression-free survival (PFS). Subgroup analyses to compare OS and PFS in patients were performed with the Cox proportional hazards model and log-rank tests. Statistical analysis was performed using SPSS Version 20 (IBM Software).

Outcome Parameters

The main outcome parameters were median overall survival (OS), hepatic progression-free survival (PFS) and safety. Overall survival (OS) was measured as the time from the first DEBIRI treatment to death. Hepatic PFS was calculated using the interval between the first DEBIRI

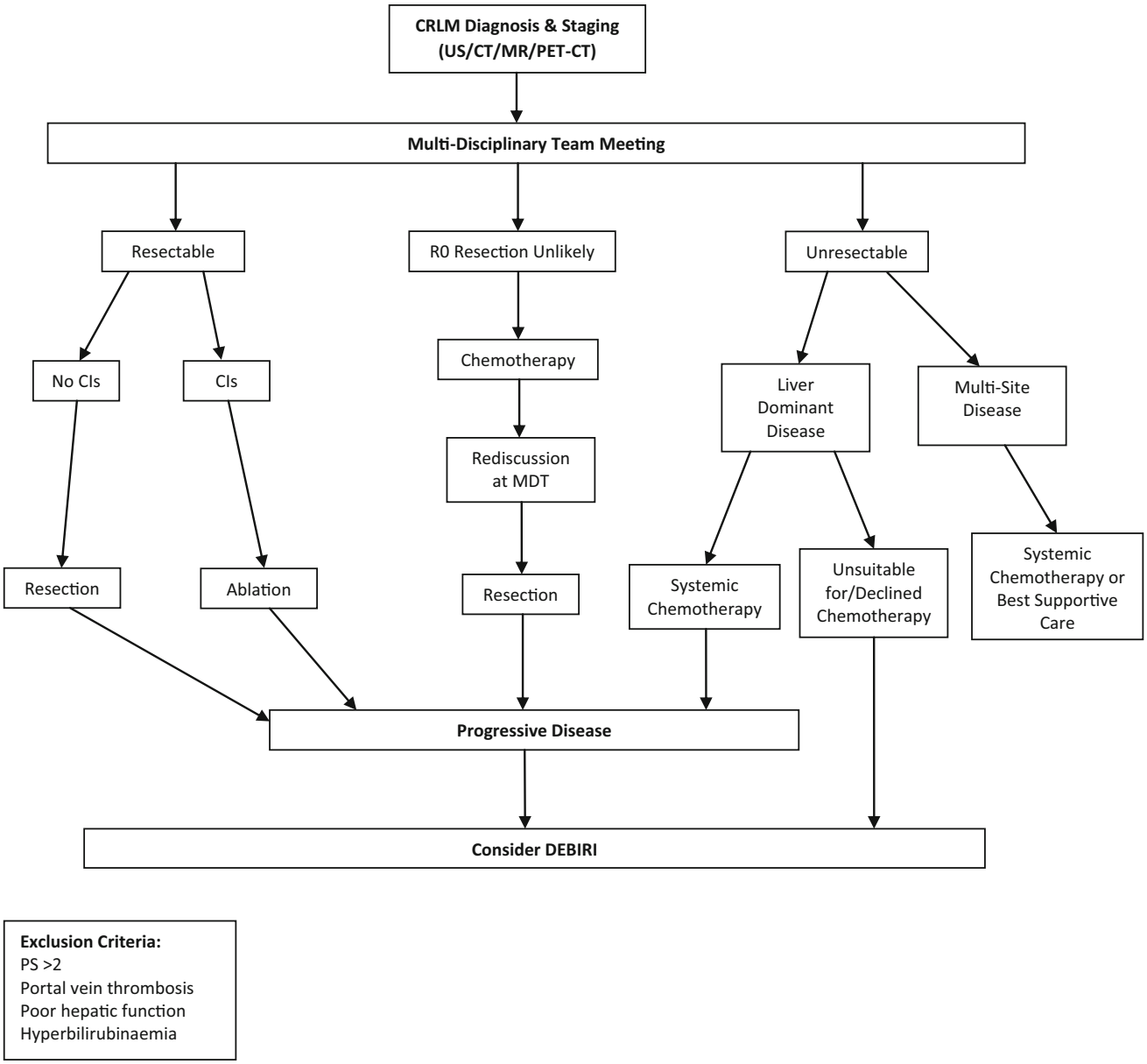

Fig. 1 Multidisciplinary team CRLM treatment pathway

treatment and the appearance of progressive disease (PD) in the liver on follow-up imaging.

Results

Patient Population

Fifty-three patients underwent 125 DEBIRI treatments during the study period. Median patient age was 71 years (range 41–88), and 39 patients (74%) were male.

At the time of treatment, 27 patients (51%) had bilobar hepatic metastases and 24 (45%) displayed extrahepatic disease, predominantly lung metastases (Table 1).

Levels of pre-treatment are summarised in Table 2. Thirty-nine patients (74%) treated had prior systemic chemotherapy. Nine patients (17%) received a systemic chemotherapy regimen containing irinotecan.

Patients received a median of 2 courses of DEBIRI. The most frequent irinotecan dose administered was 100 mg (range 50 mg–200 mg). M1 beads were used in 16 patients (30%), and M2 beads in 36 patients (68%). One patient received M2 beads during the first two treatments and M1 beads subsequently (Table 3).

Table 1 Patient and disease characteristics

	n (%)
Patient demographics	
Male	39 (74)
Age	Median 71 (41–88)
Disease characteristics	
Unilobar disease	26 (49)
Bilobar disease	27 (51)
Tumour burden	
< 25%	32 (60)
25–50%	14 (26)
51–75%	6 (11)
> 75%	1 (2)
Extrahepatic disease	
No	29 (55)
Yes	24 (45)
Site of extrahepatic disease	
Lung	20 (83)
Lymph node	2 (8)
Peritoneal	3 (13)
Brain	1 (4)

Table 2 Hepatic and systemic pre-treatment for colorectal liver metastases

	n (%)
Hepatic therapies	
Surgical resection	21 (40)
RF ablation	15 (28)
Microwave ablation	4 (8)
IRE	3 (6)
SIRT	1 (2)
Previous chemotherapy	
Yes	39 (74)
No	13 (24)
Unknown	1 (2)
Previous systemic irinotecan	9 (17)
Lines of chemotherapy	
0	13 (25)
1	16 (30)
2	10 (19)
3	10 (19)
4	2 (4)
5	1 (2)

Twenty two patients (42%) received all of their DEBIRI treatments in a lobar distribution (78 cases), and 13 patients (25%) in an exclusively selective/segmental fashion (43 cases). Seventeen patients (32%) received a mixture of lobar and selectively delivered treatments and one patient (1%) received whole liver treatment.

Table 3 Treatment delivery information

Median no. of DEBIRI treatments	2 (range 1–5)
Median irinotecan dose (mg)	100 (range 50–200)
Bead size	
M1	16 patients (30%), 61 treatments
M2	36 patients (68%), 61 treatments
Treatment delivery	
Lobar	22 (42)
Selective	13 (25)
Whole liver	17 (32)
Mixture (lobar and selective)	4 (3)

Technical Success

Of the 125 treatments, 124 were successfully delivered, giving a technical success rate of 99%. One procedure was terminated prematurely due to the patient experiencing intolerable pain during embolisation.

Overall Survival and Hepatic Progression-Free Survival

The median overall survival was 14.5 months (0.6–107), and median hepatic progression-free survival 5 months (0.2–87).

Hepatic Tumour Burden

In patients with < 25%, 2–50%, 51–75% and > 75% liver involvement by metastases, median OS was 16, 7, 5 and 3 months, and median PFS was 6.1, 5, 3.3 and 1.4 months, respectively. In patients with < 25% liver involvement by metastases ($n = 32$), median OS was 16 months compared with 6.6 months in those with > 25% involvement ($n = 21$) ($p < 0.05$). Patients with bilobar disease demonstrated inferior overall survival compared to patients with unilobar disease (median OS 8.9 months vs. 15.6 months, $p = 0.2$) (Fig. 2).

Extrahepatic Disease

Median OS in the group displaying extrahepatic disease ($n = 24$) was 10.6 months compared with 14.7 months in those with no extrahepatic disease ($n = 29$) ($p = 0.67$). PFS was 3.5 months and 6 months, respectively ($p = 0.4$) (Fig. 3).

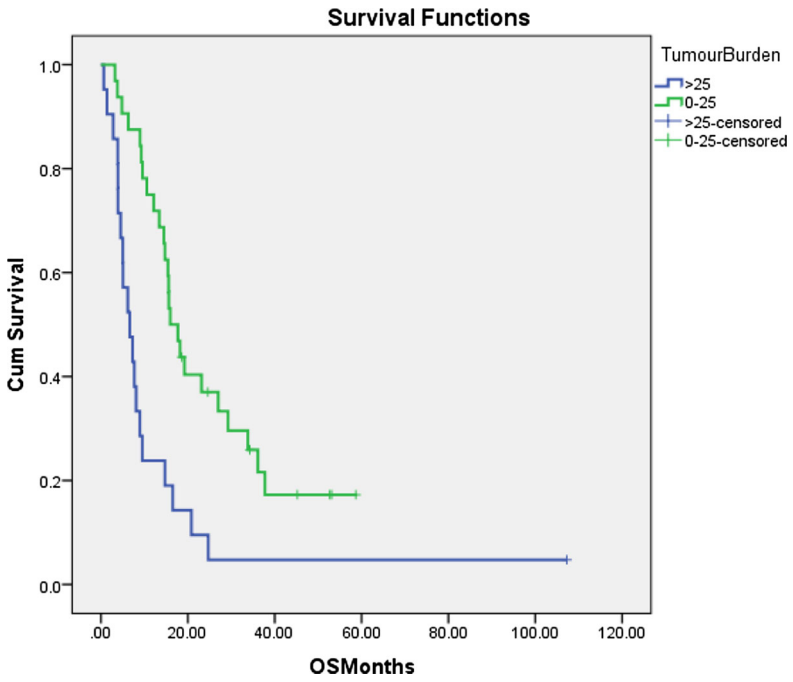

Fig. 2 Kaplan–Meier plot of overall survival by tumour burden

At Risk	0	12	24	36	48	60	72	84	96
>25	21	5	2	1	1	1	1	1	0.5
0-25	32	23.5	10	5.5	1.5				

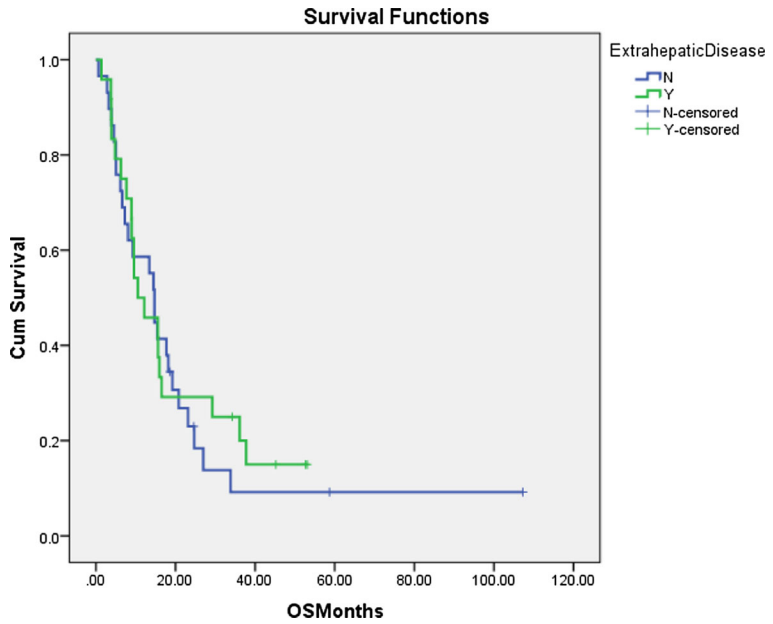

Fig. 3 Kaplan–Meier plot of overall survival by extrahepatic disease

At Risk	0	12	24	36	48	60	72	84	96
Yes	29	16.5	5.5	2	1.5	1	1	1	0.5
No	24	12	6.5	4.5	1				

Prior Ablation

Patients who received previous RF/microwave ablation or IRE (n = 21) had a median OS of 17.7 months compared with 9.5 months in those who had not (n = 32) (p = 0.09); PFS was 7 months and 3.8 months, respectively (p = 0.11) (Fig. 4).

Prior Systemic Chemotherapy

Patients previously treated with systemic chemotherapy (n = 39) had a median OS of 15.4 months compared with 9.3 months in those who had not (n = 13) ($p < 0.05$). PFS was 4.7 months and 6 months, respectively (p = 0.78).

Nine of the 39 patients who have received prior systemic chemotherapy were treated with a regimen containing irinotecan. This group demonstrated a median overall survival of 16 months compared with 13.4 months in those receiving systemic chemotherapy regimens not containing irinotecan (p = 0.5). Progression-free survival was 6.1 months in the group treated with systemic irinotecan and 5 months in those treated with other systemic chemotherapy regimens (p = 0.9) (Fig. 5, Table 4).

Bead Size

Patients treated solely with M1 beads (n = 16) displayed a median OS of 15.4 months compared with 9.5 months in those treated solely with M2 beads (n = 36) (p = 0.4). PFS was 3.8 months and 5 months, respectively (p = 0.93) (Fig. 6).

Lobar Versus Selective Treatments

Median OS in the patients treated solely with lobar DEBIRI was 7.3 months compared with 15.6 months in the group receiving solely selective DEBIRI (p = 0.25) and 18.2 months in those receiving a mixture of the two. PFS in the groups was 3, 11 and 5 months, respectively (Fig. 7).

Complications

A single procedural complication was encountered by way of dissection of the common hepatic artery which resolved by the second treatment (grade 1). Late complications included liver abscess (n = 3), biloma (n = 2) (all grade 3 on account of the requirement for intravenous antibiotics) and cholecystitis (n = 1) (grade 2). In one case, a protective embolisation coil was deployed in the right gastric artery which migrated into the coeliac trunk, just protruding into

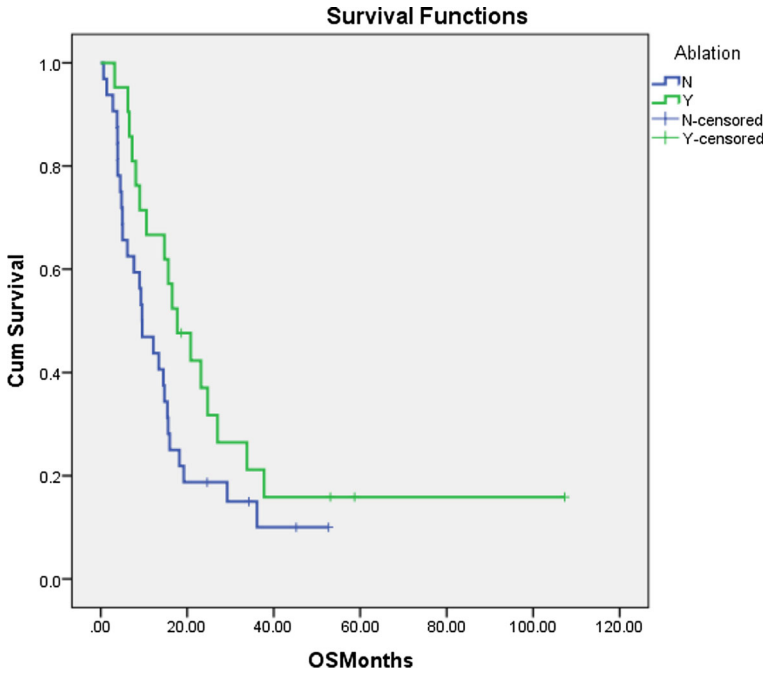

Fig. 4 Kaplan–Meier plot of overall survival by prior ablation

At Risk	0	12	24	36	48	60	72	84	96
Yes	21	13.5	7	4	2	1	1	1	0.5
No	32	15	5	2.5	0.5				

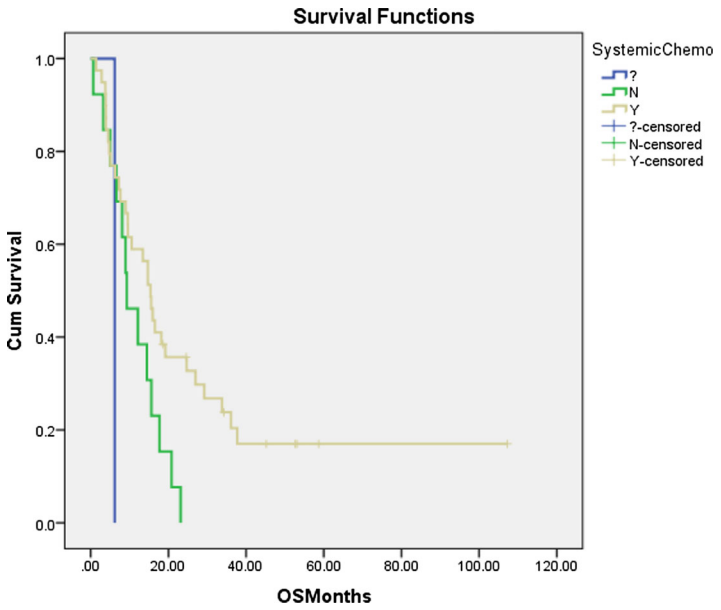

Fig. 5 Kaplan–Meier plot of overall survival by prior systemic chemotherapy

At Risk	0	12	18	24	36	48	60	72	84	96
Yes	39	22.5	15.5	12	6.5	2.5	1	1	1	0.5
No	13	6	2							

the aorta. Follow-up imaging demonstrated the coil not to have migrated further with patency of the coeliac trunk (grade 1) (Table 5). The overall complication rate was 6% (8/125).

Of the three patients that developed liver abscess post-treatment, the first had previous MWA and received two sessions of lobar-directed DEBIRI, receiving 150 mg irinotecan with M2 beads on both occasions. Liver abscess was diagnosed on CT 4 weeks post-second DEBIRI. The second had previous RFA and received two sessions of DEBIRI, the first selective and the second lobar, receiving 100 mg irinotecan on M2 beads on both occasions. They developed a liver abscess 8 weeks following the second treatment. The third patient had been treated with a metallic biliary stent 3 months prior to DEBIRI (thereby having a non-patent sphincter of Oddi) and received two sessions of DEBIRI (both selective, 100 mg irinotecan, M2 beads). Liver abscess was diagnosed on CT 8 weeks after treatment. None of the patients received prophylactic antibiotics.

Of the two patients who developed biloma, the first occurred following the patient's fifth treatment (each 100 mg irinotecan, lobar, M1 beads). The second occurred after a single DEBIRI treatment (100 mg irinotecan, lobar, M1 beads). Cholecystitis was seen in one patient treated with M1 beads in a lobar distribution.

Discussion

Our retrospective analysis of 53 patients treated with 125 courses of DEBIRI for CRLM has demonstrated a median OS of 14.5 months and hepatic PFS of 5 months.

Two prospective randomised controlled trials assessing DEBIRI in treating CRLM have been published to date. Fiorentini et al. [7] randomised 74 patients with liver-only colorectal metastases occupying less than 50% liver parenchyma who were refractory to 2–3 lines of systemic chemotherapy (none irinotecan containing) to receive DEBIRI or systemic chemotherapy (FOLFIRI). Median OS was 22 months in the DEBIRI arm versus 15 months in the FOLFIRI arm ($p = 0.031$). PFS was 7 months in the DEBIRI arm compared to 4 months in the FOLFIRI group ($p = 0.006$).

Martin et al. [6] randomised 60 patients to receive either DEBIRI with concurrent systemic modified FOLFOX ± bevacizumab ($n = 30$) or FOLFOX ± bevacizumab alone ($n = 30$) in a study to evaluate safety and tumour response rate. Patients were chemotherapy naive, had liver-dominant disease (but $< 60\%$ liver replaced by tumour) and an ECOG performance status of ≤ 2. A significant improvement in overall response rate and liver PFS was seen at 6 months in the DEBIRI group ($p = 0.05$). There was also a significantly higher rate of tumour downsizing to resection in the FOLFOX-DEBIRI arm versus the FOLFOX/bevacizumab arm (35% vs 16%, $p = 0.05$). No augmentation of chemotherapy-associated

Table 4 Subgroup analysis of treatments and outcomes

	Tumour burden			Bilobar disease			Extrahepatic disease			Previous ablation		
	< 25% (*n* = 32)	> 25% (*n* = 21)	*p*	Yes (*n* = 27)	No (*n* = 26)	*p*	Yes (*n* = 24)	No (*n* = 29)	*p*	Yes (*n* = 21)	No (*n* = 32)	*p*
Bilobar disease	12 (38)	15 (71)	0.2	n/a	n/a		15 (63)	12 (41)	0.16	8 (38)	19 (59)	0.13
Tumour burden	n/a	n/a										
< 25%				12 (44)	20 (77)		17 (71)	15 (52)		13 (62)	19 (59)	
25–50%				8 (30)	6 (23)		5 (21)	9 (31)		6 (29)	8 (25)	
50–75%				6 (22)	0		2 (8)	4 (14)		2 (10)	4 (13)	
> 75%				1 (4)	0		0	1 (3)		0	1 (3)	
Extrahepatic disease	17 (53)	7 (33)	0.16	15 (56)	9 (35)	0.13	n/a	n/a		7 (33)	17 (53)	0.16
Previous surgical resection	13 (41)	8 (38)	0.78	8 (30)	13 (50)	0.13	9 (38)	12 (41)	0.7	9 (43)	12 (38)	0.7
Previous locoregional therapy	13 (41)	8 (38)	0.78	8 (30)	13 (50)	0.13	8 (33)	14 (48)	0.13	n/a	n/a	
Prior systemic chemotherapy	25 (78)	14 (67)	0.4	22 (81)	17 (65)	0.17	21 (88)	18 (62)	0.09	14 (67)	25 (78)	0.37
Prior irinotecan systemic chemotherapy	6 (19)	3 (14)	0.44	4 (15)	5 (19)	0.57	6 (25)	3 (10)	0.28	4 (19)	5 (16)	0.69
Median no. lines of systemic chemotherapy	1	1		1	1		2	1		1	1	
Bead size												
M1	13 (41)	3 (14)		11 (41)	5 (19)		7 (29)	9 (31)		3 (14)	13 (41)	
M2	18 (56)	18 (86)		16 (59)	20 (77)		17 (71)	18 (65)		17 (81)	19 (59)	
Mixed	1 (3)	0		0	1 (4)		0	1 (3)		1 (5)	0	
Treatment location												
Lobar	20 (63)	15 (71)		15 (56)	7 (27)		10 (42)	12 (41)		8 (38)	14 (44)	
Selective	11 (34)	6 (29)		4 (15)	9 (35)		6 (25)	7 (24)		7 (33)	6 (19)	
Mixed	0	0		8 (30)	9 (35)		8 (33)	9 (31)		6 (29)	11 (34)	
Median no. of embolisations	2.5	2		2	2		2	2		2	2	
OS	16	6.6	< 0.05	8.9	15.6	0.2	10.6	14.7	0.67	17.7	9.5	0.09
PFS	6.1	3.3	0.48	7.0	3.3	< 0.05	3.5	6	0.4	7	3.8	0.11

	Prior systemic chemotherapy			Prior systemic irinotecan			Bead size			Treatment location		
	Yes (*n* = 39)	No (*n* = 13)	*p*	Yes (*n* = 9)	No (*n* = 30)	*p*	M1 (*n* = 16)	M2 (*n* = 36)	*p*	Lobar (*n* = 22)	Selective (*n* = 13)	Mixed (*n* = 17)
Bilobar disease	22 (56)	4 (31)	0.17	4 (44)	18 (60)	0.41	11 (69)	16 (44)	0.16	15 (68)	4 (31)	8 (47)
Tumour burden												
< 25%	25 (64)	7 (54)		6 (67)	19 (63)		13 (81)	18 (50)		11 (50)	8 (62)	12 (71)
25–50%	8 (21)	5 (38)		2 (22)	6 (30)		1 (6)	13 (36)		8 (36)	4 (31)	2 (12)
50–75%	5 (13)	1 (8)		1 (11)	4 (13)		2 (13)	4 (11)		2 (9)	1 (8)	3 (18)
> 75%	1 (3)	0		0	1 (3)		0	1 (3)		1 (5)	0	0
Extrahepatic disease	21 (54)	3 (23)	0.1	6 (67)	15 (50)	0.38	7 (44)	17 (47)	0.64	10 (45)	6 (46)	8 (47)
Previous surgical resection	16 (41)	5 (38)	0.71	3 (33)	13 (43)	0.59	3 (19)	18 (50)	0.08	10 (45)	6 (46)	5 (29)
Previous locoregional therapy	14 (36)	7 (54)	0.37	4 (44)	10 (33)	0.54	3 (19)	17 (47)	0.07	8 (36)	7 (54)	6 (35)

Table 4 continued

	Prior systemic chemotherapy			Prior systemic irinotecan			Bead size			Treatment location		
	Yes (n = 39)	No (n = 13)	p	Yes (n = 9)	No (n = 30)	p	M1 (n = 16)	M2 (n = 36)	p	Lobar (n = 22)	Selective (n = 13)	Mixed (n = 17)
Prior systemic chemotherapy	n/a	n/a		n/a	n/a		16 (100)	23 (64)	0.03	16 (73)	8 (62)	14 (82)
Prior irinotecan systemic chemotherapy	n/a	n/a		n/a	n/a		4 (25)	5 (14)	0.81	2 (9)	3 (23)	4 (24)
Median no. lines of systemic chemotherapy	2	–		2	1.5		1	2		1	1	2
Bead size							n/a	n/a				
M1	16 (41)	0		4 (44)	12 (40)					6 (27)	2 (15)	7 (41)
M2	23 (59)	12 (92)		5 (56)	18 (60)					16 (73)	11 (85)	9 (53)
Mixed	0	1 (8)		0	0					0	0	1 (6)
Treatment location										n/a	n/a	n/a
Lobar	16 (41)	5 (38)		2 (22)	14 (47)		6 (38)	16 (44)				
Selective	8 (21)	5 (38)		2 (33)	5 (17)		2 (13)	11 (31)				
Mixed	14 (36)	3 (23)		4 (44)	10 (33)		7 (44)	9 (25)				
Median no. of embolisations	2	2		2	2		3.5	1		1	1	3
OS	15.4	9.3	< 0.05	16	13.4	0.5	15.4	9.5	0.4	7.3	15.6	18.2
PFS	4.7	6	0.78	6.1	5	0.9	3.8	5	0.93	3	11	5

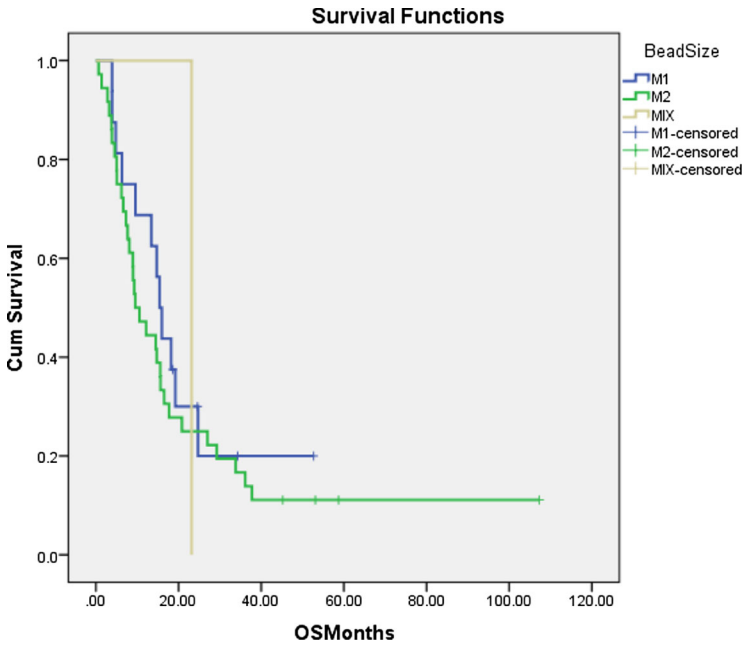

Fig. 6 Kaplan–Meier plot of overall survival by bead size

At Risk	0	12	24	36	48	60	72	84	96
M1	16	10.5	3	1	0.5				
M2	36	17	9	5.5	2	1	1	1	0.5
Mix	1	1							

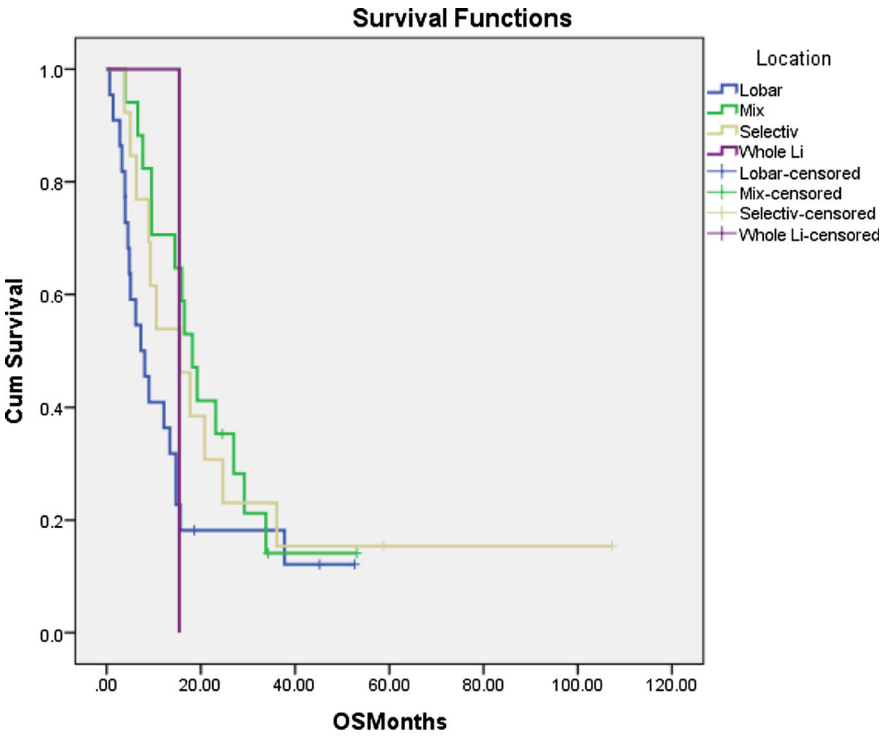

Fig. 7 Kaplan–Meier plot of overall survival by treatment location

At Risk	0	12	24	36	48	60	72	84	96
Lobar	22	8.5	3	2.5	0.5				
Mix	17	12	5	1	0.5				
Selective	13	7	4	3	1.5	1	1	1	0.5
Whole Liver	1	1							

Table 5 Complications

	n
Dissection of common hepatic artery	1
Coil migration	1
Liver abscess	3
Biloma	2
Cholecystitis	1

adverse events was noted in patients treated with DEBIRI and FOLFOX concurrently.

We have demonstrated less favourable survival outcome in patients carrying a larger hepatic tumour burden, as well as those with bilobar disease. These trends have previously been well demonstrated [8–10].

The presence of extrahepatic disease in our cohort was also seen to adversely affect survival. This is in contrast to Huppert et al. who saw no impact on survival by the presence of extrahepatic metastases [10], although previous registry data have shown it to be a predictor of overall survival [11]. In our cohort, patients with extrahepatic disease were more likely to display bilobar disease and less likely to have received previous locoregional therapy, indicating a heavier disease burden, which is likely to have influenced this finding.

In our study, patients who received previous RF ablation, microwave ablation or IRE displayed significantly superior overall survival over patients having had no such previous hepatic procedures. The notion that resection or ablation may synergistically enhance DEBIRI has not been formally studied; however, the trend has been previously described [9]. In our cohort, patients treated with ablation had a lower overall burden of disease with a lower incidence of bilobar and extrahepatic disease, which is likely to have influenced this finding.

We observed a significant increase in survival in patients previously treated with systemic chemotherapy when compared to chemotherapy naive patients. This was despite these patients displaying a greater incidence of extrahepatic disease and a greater burden of hepatic disease in terms of tumour volume and bilobar disease. We believe the treatment of patients with DEBIRI in a ‘salvage’ setting who were deemed unfit for systemic chemotherapy may have

influenced this finding. In addition, some heavily pre-treated patients who remained fit enough to receive DEBIRI might represent a subset of patients displaying greater resilience to their disease, or possibly less aggressive tumour biology. We saw no survival disadvantage in patients who were refractory to systemic irinotecan.

Bhutiani et al. [12], in their multicentre registry data including 192 DEBIRI treatments in patients who received prior systemic irinotecan and 222 treatments in irinotecan-naive patients, concluded that the safety and efficacy of DEBIRI were not affected by non-response to prior systemic chemotherapy regimens containing irinotecan.

A trend towards greater overall survival was seen in patients treated with M1 beads compared with those treated with M2 beads. Patients treated with M2 beads in our study displayed a heavier burden of hepatic disease in terms of tumour volume which may have influenced survival. Patients treated with M2 beads were also more heavily pre-treated with surgical resection and ablation, although a significantly greater proportion of those treated with M1 beads had prior systemic chemotherapy. The possible advantages of utilising smaller (M1) beads in DEBIRI have previously been investigated by Akinwande et al. [13]. The study demonstrated greater dose delivery in patients treated with M1 beads compared to M2, and the authors postulate M1 beads to have a lower propensity to reach complete stasis than the M2. There was also a trend towards lower toxicity with the smaller bead. In our cohort, patients treated with M1 beads received a median of 3.5 embolisations compared with 1 in patients treated with M2 beads; however, no data was collected regarding the embolisation end point in our study.

In our cohort, patients treated solely with lobar-directed DEBIRI displayed inferior overall survival when compared to those treated only with selective/segmental embolisation (7.3 months vs 15.6 months, respectively). Lobar-directed treatments were administered to patients with a greater hepatic disease burden which is likely to have influenced survival. Given our limited cohort size, we were unable to perform a meaningful subgroup analysis to compare outcomes between patients treated with lobar and selective DEBIRI depending on hepatic tumour burden. Technical recommendations produced by Lencioni et al. [7] suggest delivering lobar-directed treatments in order to treat sub-clinical metastases which may not manifest at the time of pre-treatment imaging. Furthermore, lobar administration of DEBIRI may be crucial in maximising its biologic effect. Irinotecan is a semi-synthetic analogue of camptothecin, a prometabolite converted by the enzymes carboxylesterase-1 and -2 into its active form SN-38 [14]. The process occurs predominantly within normal liver cells which display far greater expression of the enzymes than within solid tumours. Thus, by delivering the drug super selectively within tumoural tissue, its activation may only occur unintentionally via osmosis of the drug into normal hepatic parenchyma [15].

Our technical success rate of 99% and complication rate of 6% add to the growing body of literature to support DEBIRI as a safe treatment. Adverse effects have been found to be uncommon with DEBIRI, the most widely reported being post-embolisation syndrome and hypertension, which is self-limiting [16]. The development of liver abscess following DEBIRI has been previously described in one series of 40 patients by Fiorentini et al. [17]. We observed liver abscesses to occur in three patients. None of these patients received prophylactic antibiotics. The routine use of prophylactic antibiotics in TACE is not advocated in patients with native biliary anatomy [18]; however, a strong association with the development of liver abscess following TACE in patients with bilio-enteric anastomoses has been reported [19]. Biloma occurred in two patients both treated with M1 beads. The safety of M1 beads in TACE in the context of HCC has been well established [20], although an association of the use of M1 beads with an increase in hepatobiliary adverse events including biloma and cholecystitis has been described [21].

Limitations

Our retrospective analysis has several limitations. The statistical significance demonstrated in our findings is limited by the small cohort size, further compounded by heterogeneity within the group in terms of disease severity (including the presence of extrahepatic disease), performance status and levels of pre-treatment. However, we feel this reflects the inherently complex ‘real world’ patient population discussed at our multidisciplinary team meetings who are considered for DEBIRI, a treatment which in our practice is not infrequently administered in a ‘salvage’ setting.

Institutional variations in treatment delivery, including anaesthesia, choice of bead size and treatment location introduced added heterogeneity to the dataset which may have influenced outcomes.

Performance status data were not recorded in our study which may have provided a useful marker with which to compare subgroups which displayed similar levels of disease, which may have aided in resolving discrepancies in outcome. Lastly, any treatments the patients may have received following DEBIRI were not accounted for in this study which may have influenced outcome.

Conclusion

Our findings add to a small but growing number of studies to have demonstrated encouraging outcomes with the use of DEBIRI. However, the current body of evidence for

DEBIRI remains heterogeneous in both patient selection and treatment technique and further randomised controlled trials are necessary to establish the optimum berth for DEBIRI in CRLM treatment. Further studies to investigate its potential value as a first-line treatment with concomitant systemic chemotherapy would be welcomed, as well as randomised trials to establish comparative outcomes with other locoregional therapies currently in use such as selective internal radiation therapy (SIRT).

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Human and Animal Rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed Consent For this type of study formal consent is not required.

References

1. Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11. Lyon: International Agency for Research on Cancer; 2013. http://globocan.iarc.fr. Accessed 1 July 2018.
2. Gruber-Rouh T, Naguib N, Eichler K, et al. Transarterial chemoembolization of unresectable systemic chemotherapy-refractory liver metastases from colorectal cancer: long-term results over a 10-year period. Int J Cancer. 2014;134(5):1225–31. https://doi.org/10.1002/ijc.28443.
3. Fong Y, Blumgart LH. Hepatic colorectal metastasis: current status of surgical therapy. Oncology. 1998;12:1489–503.
4. Aliberti C, Tilli M, Benea G, Fiorentini G. Trans-arterial chemoembolization (TACE) of liver metastases from colorectal cancer using irinotecan-eluting beads: preliminary results. Anticancer Res. 2006;26:3793–5.
5. Akinwande O, Scoggins C, Martin RC. Early experience with 70–150 μm irinotecan drug-eluting beads (M1-DEBIRI) for the treatment of unresectable hepatic colorectal metastases. Anticancer Res. 2016;36(7):3413–8.
6. Martin R, Scoggins C, Schreeder M, et al. Randomized controlled trial of irinotecan drug-eluting beads with simultaneous FOLFOX and bevacizumab for patients with unresectable colorectal liver-limited metastasis. Cancer. 2015;121(20):3649–58.
7. Lencioni R, Aliberti C, de Baere T, Garcia-Monaco R, Narayanan G, O'Grady E, Rilling WS, Walker D, Martin RC. Transarterial treatment of colorectal cancer liver metastases with irinotecan-loaded drug-eluting beads: technical recommendations. J Vasc Interv Radiol. 2014;25(3):365–9. https://doi.org/10.1016/j.jvir.2013.11.027.
8. Fiorentini G, Aliberti C, Tilli M, et al. Intra-arterial infusion of irinotecan-loaded drug-eluting beads (DEBIRI) versus intravenous therapy (FOLFIRI) for hepatic metastases from colorectal cancer: final results of a phase III study. Anticancer Res. 2012;32(4):1387–95.
9. Stutz M, Mamo A, Valenti D, et al. Real-life report on chemoembolization using DEBIRI for liver metastases from colorectal cancer. Gastroenterol Res Pract. 2015;2015:715102. https://doi.org/10.1155/2015/715102.
10. Huppert P, Wenzel T, Wietholtz H. Transcatheter arterial chemoembolization (TACE) of colorectal cancer liver metastases by irinotecan-eluting microspheres in a salvage patient population. Cardiovasc Intervent Radiol. 2014;37(1):154–64. https://doi.org/10.1007/s00270-013-0632-0.
11. Martin R, Robbins K, Tomalty D, et al. Transarterial chemoembolisation (TACE) using irinotecan-loaded beads for the treatment of unresectable metastases to the liver in patients with colorectal cancer: an interim report. World J Surg Oncol. 2009;7:80. https://doi.org/10.1186/1477-7819-7-80.
12. Bhutiani N, Akinwande O, Martin R. Efficacy and toxicity of hepatic intra-arterial drug-eluting (Irinotecan) Bead (DEBIRI) therapy in irinotecan-refractory unresectable colorectal liver metastases. World J Surg. 2016;40(5):1178–90. https://doi.org/10.1007/s00268-015-3386-9.
13. Akinwande O, Philips P, Duras P, Pluntke S, Scoggins C, Martin R. Small versus large-sized drug-eluting beads (DEBIRI) for the treatment of hepatic colorectal metastases: a propensity score matching analysis. Cardiovasc Intervent Radiol. 2015;38(2):361–71. https://doi.org/10.1007/s00270-014-1011-1.
14. Young S, D'Souza D, Flanagan S, et al. Review of the clinical evidence for the use of DEBIRI in the treatment of colorectal metastatic disease. Cardiovasc Intervent Radiol. 2017;40:496. https://doi.org/10.1007/s00270-016-1537-5.
15. Liu D, Thakor A, Baerlocher M, Alshammari M, Lim H, et al. A review of conventional and drug-eluting chemoembolization in the treatment of colorectal liver metastases: principles and proof. Future Oncol. 2015;11(9):1421–8. https://doi.org/10.2217/fon.15.3.
16. Richardson A, Laurence J, Lam V. Transarterial chemoembolization with irinotecan beads in the treatment of colorectal liver metastases: systematic review. J Vasc Interv Radiol. 2013;24(8):1209–17. https://doi.org/10.1016/j.jvir.2013.05.055.
17. Fiorentini G, Aliberti C, Turrisi G, et al. Intra-arterial hepatic chemoembolisation of liver metastases from colorectal cancer adopting irinotecan-eluting beads: results of a phase III clinical study. Vivo. 2007;21(1085):1092.
18. Watchmaker J, Lipnik A, Fritsche M, Baker J, Mouli S, Geevarghese S, Banovac F, Omary R, Brown D. Are prophylactic antibiotics necessary prior to transarterial chemoembolization for hepatocellular carcinoma in patients with native biliary anatomy? J Surg Oncol. 2018;117(6):1312–7. https://doi.org/10.1002/jso.24993.
19. Woo S, Chung J, Hur S, Joo S, Kim H, Jae H, Park J. Liver abscess after transarterial chemoembolization in patients with bilioenteric anastomosis: frequency and risk factors. AJR Am J Roentgenol. 2013;200(6):1370–7. https://doi.org/10.2214/AJR.12.9630.
20. Spreafico C, Cascella T, Facciorusso A, Sposito C, Rodolfo L, Morosi C, Civelli EM, Vaiani M, Bhoori S, Pellegrinelli A, Marchianò A, Mazzaferro V. Transarterial chemoembolization for hepatocellular carcinoma with a new generation of beads: clinical-radiological outcomes and safety profile. Cardiovasc Intervent Radiol. 2015;38(1):129–34. https://doi.org/10.1007/s00270-014-0907-0.
21. Deipolyi AR, Oklu R, Al-Ansari S, Zhu A, Goyal L, Ganguli S. Safety and efficacy of 70–150 μm and 100–300 μm drug-eluting bead transarterial chemoembolization for hepatocellular carcinoma. J Vasc Interv Radiol. 2015;26(4):516–22.