Ann Surg Oncol (2019) 26:275–281
https://doi.org/10.1245/s10434-018-6945-0

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Intrahepatic Recurrence Patterns Predict Survival After Resection of Colorectal Liver Metastases

Andrew J. Lee, MD, PhD[1], Evelyne M. Loyer, MD[2], Hyunseon C. Kang, MD[2], Thomas A. Aloia, MD[1], Ching-Wei D. Tzeng, MD[1], Jean-Nicolas Vauthey, MD[1], and Yun Shin Chun, MD[1]

[1]Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; [2]Department of Diagnostic Radiology, The University of Texas MD Anderson Cancer Center, Houston, TX

ABSTRACT

Background. After resection of colorectal liver metastases (CLM), up to 40% of patients will develop intrahepatic recurrence. This study aims to identify patterns of intrahepatic recurrence and their impact on survival after preoperative chemotherapy and CLM resection.

Methods. A retrospective review was performed of patients developing intrahepatic recurrence after CLM resection following preoperative chemotherapy. Prechemotherapy, preoperative, and postoperative computed tomography scans were reviewed. Recurrences were classified as in situ, de novo, or both in situ and de novo. Median follow-up was 42 months (range 2–144 months).

Results. Among 223 patients meeting study criteria, intrahepatic recurrence was identified a median of 9 months after hepatectomy. Isolated de novo or in situ recurrence developed in 105 (47%) and 86 (39%) patients, respectively. Thirty-two patients (14%) developed both in situ and de novo recurrence, which was associated with significantly lower median overall survival of 33 months compared with 49 and 45 months with isolated in situ or de novo recurrence, respectively ($p = 0.048$). Among 118 patients (53%) who developed in situ recurrence as a component of disease relapse, recurrences resulted from disappearing or missed liver metastases in 47 patients (40%).

Conclusions. An intrahepatic recurrence pattern of both in situ and de novo metastases after CLM resection following preoperative chemotherapy predicts significantly worse overall survival compared with isolated in situ or de novo recurrence.

First Received: 19 July 2018;
Published Online: 25 October 2018

Y. S. Chun, MD
e-mail: yschun@mdanderson.org

Colorectal cancer is the third highest cause of cancer-related mortality in the USA, and most patients dying of colorectal cancer will have liver metastases.[1] Owing to advances in systemic therapy, surgical technique, and diagnostic and interventional radiology, more patients are eligible for hepatic resection with curative intent, which is associated with a 5-year overall survival rate of 58%.[2] However, after hepatic resection, 50–70% of patients will suffer disease relapse, most commonly in the remnant liver.[3] Prior studies have examined all sites of disease relapse after resection of colorectal liver metastases (CLM) and demonstrated that isolated liver or pulmonary recurrence is associated with better survival than multiple sites of disease failure.[4,5]

For patients who develop intrahepatic recurrence, the prognostic significance of in situ compared with de novo metastases is not well established. Recognizing patterns of intrahepatic recurrence and their prognostic implications can potentially inform surgical strategies to prevent in situ relapse and guide therapy for recurrent disease. The aims of this study are to analyze patients who developed intrahepatic recurrence after CLM resection following preoperative chemotherapy and to determine survival outcomes based on patterns and treatment of intrahepatic recurrence.

PATIENTS AND METHODS

Patients

From 819 patients undergoing CLM resection after preoperative chemotherapy at the University of Texas MD

Anderson Cancer Center between 2004 and 2011, 223 patients suffered disease relapse in the liver as a component of first recurrence and had prechemotherapy, preoperative, and postoperative computed tomography (CT) imaging available. Computerized medical records were reviewed for data on clinicopathological factors, tumor recurrence, and patient survival. Major hepatectomy was defined as anatomic resection of three or more Couinaud segments.[6] The number and diameter of liver metastases were determined from surgical pathology specimens. R1 resection margin was defined as tumor cells < 1 mm of the transection line.

Pre- and postoperative chemotherapy was administered at the discretion of treating providers. Our institutional practice is to administer short-course preoperative chemotherapy to most patients before liver resection, followed by postoperative chemotherapy to complete 6 months total of systemic therapy.[7] Selection criteria for liver resection include sufficient future liver remnant volume and technical resectability, as previously described.[8,9] Patients with insufficient future liver remnant volume underwent portal vein embolization.[10] Two-stage hepatectomy, with our without portal vein embolization, was performed in patients with bilateral metastases that could not be safely resected in one stage.[11] Patients with extrahepatic disease were considered for surgery if all sites of disease could be resected, or if patients had indeterminate or disappearing lung lesions.

This study was approved by the institutional review board at the University of Texas MD Anderson Cancer Center.

CT Technique and Analysis

Triphasic liver protocol CT scans included an unenhanced evaluation of the liver, followed by images obtained 30, 50, and 70 s after the start of intravenous injection of ioversol at rate of 5 mL/s. Image reconstruction thicknesses used for diagnostic interpretation were 2.5 and 5 mm.

Recurrence

Disease recurrence was recorded as the first site(s) of relapse after initial hepatectomy. In situ intrahepatic recurrence was defined as metastases visible on CT before chemotherapy or developing at the margin of prior resection or ablation. De novo recurrence was defined as new tumors remote from the site of metastases identified on prechemotherapy and preoperative CT scans.

Statistical Analysis

Comparisons between groups were analyzed using the Chi squared test for categorical data and Mann–Whitney test for continuous variables. Overall survival was calculated from date of initial hepatic resection, unless otherwise specified. For patients undergoing two-stage hepatectomy, survival was calculated from date of the second-stage hepatectomy. Survival was estimated by Kaplan–Meier method, and comparisons between groups were performed using the log-rank test. p value < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS Statistics 24.0 (IBM Corporation, Armonk, NY, USA). Data are presented as median (range), unless otherwise specified.

RESULTS

Patients

Among 819 patients undergoing CLM resection after preoperative chemotherapy, 223 patients developed intrahepatic disease relapse as a component of first recurrence and had prechemotherapy, preoperative, and postoperative CT imaging available. In addition to preoperative CT, 24 of the 223 patients (11%) underwent magnetic resonance imaging (MRI). Clinicopathologic factors of the 223 patients are listed in Table 1. Resection of a solitary liver metastasis was performed in 46 patients (21%) and multiple CLM in 177 patients (79%). Most patients received FOLFOX and bevacizumab preoperatively. At time of initial hepatic resection, 37 patients (17%) had extrahepatic disease, most commonly in the lungs ($n = 18$) and portal lymph nodes ($n = 6$).

Patterns of Recurrence

The initial recurrence involved the liver only in 137 patients (61%) and liver and extrahepatic sites in 86 patients (39%). Sites of extrahepatic metastases were the lungs ($n = 43$), intraabdominal and/or retroperitoneal lymph nodes ($n = 14$), peritoneum ($n = 9$), bone ($n = 1$), colon ($n = 1$), and multiple sites ($n = 18$).

Intrahepatic recurrences were classified as de novo in 105 patients (47%), in situ in 86 patients (39%), and both de novo and in situ in 32 patients (14%). Among the 118 patients with in situ recurrence as a component of disease relapse, reasons for local failure were disappearing or missed metastases in 47 patients (40%), marginal recurrence after resection in 55 patients (47%), and local tumor progression after ablation in 16 patients (13%).

TABLE 1 Clinicopathologic factors of 223 patients developing intrahepatic recurrence after resection of colorectal liver metastases following preoperative chemotherapy

Factor	*n* (%)
Median age (range), years	58 (25–82)
Gender	
Male	141 (63)
Female	82 (37)
Primary tumor	
Colon	178 (80)
Rectum	45 (20)
Preoperative chemotherapy	
Oxaliplatin based	164 (74)
Irinotecan based	41 (18)
Both oxaliplatin and irinotecan	13 (6)
5-Fluorouracil or capecitabine alone	5 (2)
Preoperative biologic agents	
Anti-VEGF	163 (73)
Anti-EGFR	10 (4)
Both anti-VEGF and anti-EGFR	9 (4)
None	41 (18)
Median duration of preoperative chemotherapy (range), months	3 (1–31)
Postoperative chemotherapy	128 (57)
Node-positive primary tumor[a]	167 (80)
Bilateral metastases	151 (68)
Two-stage resection	27 (12)
Portal vein embolization	39 (17)
Extrahepatic metastases at time of hepatectomy	37 (17)
Major hepatectomy	143 (64)
Concomitant radiofrequency ablation	46 (21)
Resection margin	
R0	174 (78)
R1	49 (22)
Median diameter of largest metastasis (range), cm	2.5 (0.3–15.0)
Median number of liver metastases (range)	3 (1–76)

VEGF vascular endothelial growth factor, *EGFR* epidermal growth factor receptor

[a]Data not available in 15 patients

Patterns of Intrahepatic Recurrence and Overall Survival

For all patients, median follow-up was 42 months (range 2–144 months); median and 5-year overall survival rates were 44 months [95% confidence interval (CI) 39–49 months] and 34%. Among patients with both de novo and in situ recurrence, median and 5-year overall survival rates were 33 months (95% CI 21–45 months) and 24%, compared with 45 months (95% CI 35–55 months) and 34% with isolated de novo recurrence, and 49 months

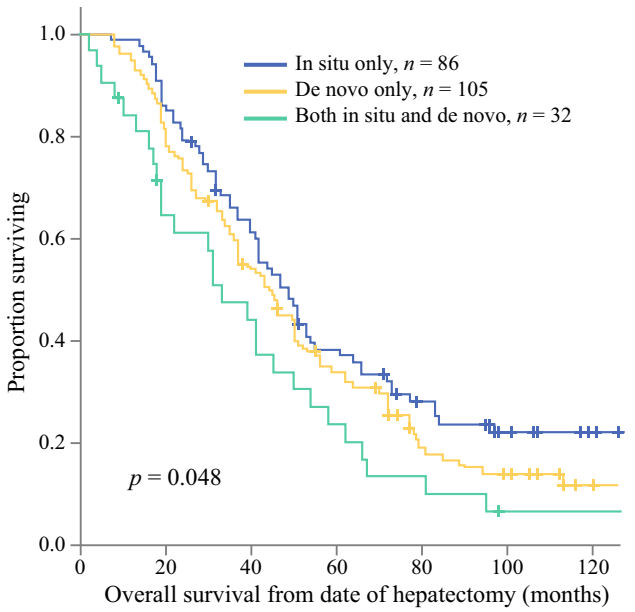

FIG. 1 Overall survival from date of hepatic resection, stratified by pattern of intrahepatic recurrence

(95% CI 41–57 months) and 38% with isolated in situ recurrence (Fig. 1, $p = 0.048$).

Median time to recurrence was 9 months for all patients and not significantly different based on patterns of intrahepatic recurrence. Median recurrence-free survival was 8 months (95% CI 7–9 months) with de novo recurrence, 9 months (95% CI 7–11 months) with in situ recurrence, and 6 months (95% CI, 3–9 months) with both de novo and in situ recurrence ($p = 0.065$).

Factors at the initial hepatic resection significantly associated with development of both de novo and in situ intrahepatic recurrence were R1 margin, concomitant ablation, bilateral liver metastases, > 1 liver metastasis, and duration of preoperative chemotherapy ≥ 6 months (Table 2).

On multivariable analysis, pattern of intrahepatic recurrence as both de novo and in situ recurrence was an independent predictor of overall survival (Table 3). Other factors independently associated with overall survival were extrahepatic disease at time of hepatectomy and size of largest metastasis > 5 cm.

Extrahepatic Recurrence

Disease relapse in both the liver and extrahepatic sites occurred in 45% (47 of 105) of patients with de novo intrahepatic recurrence, 37% (23 of 63) of patients with in situ recurrence, and 50% (16 of 32) of patients with both de novo and in situ recurrence ($p = 0.014$).

TABLE 2 Factors associated with pattern of intrahepatic recurrence in 223 patients, n (%)

	De novo, n = 105	In situ, n = 86	Both de novo and in situ, n = 32	p
Major hepatectomy	72 (69)	52 (60)	19 (59)	0.424
Two-stage hepatectomy	12 (11)	9 (10)	6 (19)	0.452
R1 margin	19 (18)	17 (20)	13 (41)	0.022
Ablation during liver resection	11 (18)	24 (28)	11 (34)	0.001
Bilateral liver metastases	62 (59)	62 (72)	27 (84)	0.015
> 1 liver metastasis	88 (84)	61 (71)	28 (88)	0.043
Extrahepatic disease at time of hepatectomy	22 (21)	9 (10)	6 (19)	0.143
Duration of preoperative chemotherapy ≥ 6 months	16 (15)	25 (29)	14 (44)	0.002
Diameter of largest metastasis > 5 cm	18 (17)	10 (12)	9 (28)	0.099
Receipt of postoperative chemotherapy	63 (60)	46 (53)	19 (59)	0.644

Treatment of Intrahepatic Recurrence

Treatment of intrahepatic recurrence included surgery or ablation in 79 patients, chemotherapy alone in 124 patients, and chemotherapy plus external-beam radiation or yttrium-90 radioembolization in 13 patients. Seven patients received best supportive care. Median and 3-year overall survival rates from date of initial intrahepatic recurrence were 59 months (95% CI 51–67 months) and 74% for patients undergoing repeat hepatectomy or ablation, 25 months (95% CI 19–31 months) and 32% with chemotherapy alone, 37 months (95% CI 11–63 months) and 51% with chemotherapy plus radiotherapy, and 5 months (95% CI 1–7 months) and 0% with best supportive care (Fig. 2, $p < 0.001$).

Repeat hepatectomy or ablation was performed in 42% (36 of 86) of patients with in situ recurrence, 33% (35 of 105) of patients with de novo recurrence, and 25% (8 of 32) of patients with both in situ and de novo recurrence ($p = 0.19$).

DISCUSSION

Despite advances in surgical technique and perioperative chemotherapy, and improved patient selection, relapse in the remnant liver occurs in up to 40% of patients after resection of CLM.[12] Recognizing patterns of intrahepatic recurrence and their prognostic significance is important in informing surgical strategy at the initial hepatectomy to potentially prevent remnant liver recurrence and to guide treatment decisions for recurrent disease. The aims of this study are to analyze patients whose initial site(s) of recurrence after preoperative chemotherapy and CLM resection involved the liver and to identify patterns of intrahepatic recurrence and their effects on patient survival.

In this study, a minority of patients (14%) developed both in situ and de novo intrahepatic recurrence compared with isolated in situ (39%) or de novo (47%) relapse. Factors at initial hepatectomy that correlated with development of both in situ and de novo recurrence were multiple, bilateral metastases, receipt of ≥ 6 months of chemotherapy, R1 margin, and concomitant ablation. Extrahepatic disease as a component of disease failure occurred in more patients with both de novo and in situ intrahepatic recurrence (50%) than patients with isolated in situ (37%) or de novo (45%) recurrence. The median overall survival rate with both in situ and de novo intrahepatic recurrence was 33 months compared with 45 and 49 months with isolated de novo or in situ recurrence, respectively. These data support prior studies showing that local intrahepatic recurrence alone does not determine survival.[13,14] On the other hand, disseminated disease in the form of both in situ and de novo intrahepatic recurrence, compounded by extrahepatic disease, signals poor tumor biology and worse patient survival.

Recurrent liver metastases after CLM resection are hypothesized to represent progression of disease overlooked at the first liver resection.[15] In this report, 53% of patients developed in situ intrahepatic recurrence, resulting from disappearing or missed metastases, marginal recurrence, or progression after ablation. Other studies have shown low rates of local failure after hepatic resection, ranging from 2 to 4%.[2,16] The high rate of local recurrence in the present study is attributable to careful review of prechemotherapy imaging for disappearing or missed liver metastases. Furthermore, the current analysis is limited to only patients who suffered intrahepatic disease relapse, in contrast to prior studies that evaluated all patients undergoing CLM resection.

TABLE 3 Multivariable overall survival analysis of 223 patients who developed intrahepatic recurrence after resection of colorectal liver metastases

Factor	*n*	Median OS, months	5-year OS (%)	Univariable *p*	Multivariable *p*	Hazard ratio
Age				0.705		
Gender				0.740		
Male	141	43	31			
Female	82	45	39			
Extrahepatic disease at time of hepatectomy				0.011	0.012	1.63 (1.12–2.39)
Yes	37	33	19			
No	186	46	37			
> 1 liver metastasis				0.091		
Yes	177	42	30			
No	46	56	50			
Diameter of largest metastasis > 5 cm				< 0.001	0.006	1.74 (1.17–2.57)
Yes	37	27	20			
No	186	47	37			
Two-stage hepatectomy				0.864		
Yes	27	43	28			
No	196	44	35			
Major hepatectomy				0.009	0.050	1.38 (1.00–1.91)
Yes	143	40	29			
No	80	52	43			
Radiofrequency ablation				0.198		
Yes	46	43	24			
No	177	45	37			
Resection margin				0.118		
R0	174	45	36			
R1	49	42	29			
Pattern of intrahepatic recurrence				0.030	0.030	1.58 (1.05–2.38)
De novo or in situ	191	46	36			
Both de novo and in situ	32	33	24			

OS overall survival

In situ intrahepatic recurrence resulted from disappearing or missed metastases in 40% of patients and marginal recurrence in 47% of patients. A report by Owen et al. categorized metastases not visualized on intraoperative ultrasound but retrospectively identified on MRI as missed metastases.[14] Such metastases were typically multiple, small, and not individually identified in radiology reports. Recurrence of disappearing or missed CLM underscores the need for annotation of individual metastases and resection of all metastases visualized on prechemotherapy imaging.[13] The current study shows that marginal recurrence represents a significant cause of disease failure. Although the necessary width of negative resection margin is controversial, most series demonstrate that a positive margin is an independent predictor of worse survival.[16,17] Taken together, these results highlight the importance of high-quality imaging, particularly before chemotherapy, and negative margins at the initial hepatectomy to avoid preventable recurrences.

Intraoperative ablation at time of initial hepatectomy was significantly associated with development of both in situ and de novo intrahepatic recurrence. A study by Abdalla et al. observed an intrahepatic recurrence rate of 28% after concomitant ablation and resection compared with 11% after resection alone.[2] Brouquet and colleagues analyzed 28 patients who underwent resection of postablation CLM recurrence, including in situ recurrence in 22 patients, de novo metastases in 2 patients, and both in situ and de novo recurrence in 4 patients.[18] Resection after prior ablation was associated with significant 90-day postoperative morbidity and mortality rates of 46% and 7%, respectively. Twelve of the 28 patients underwent

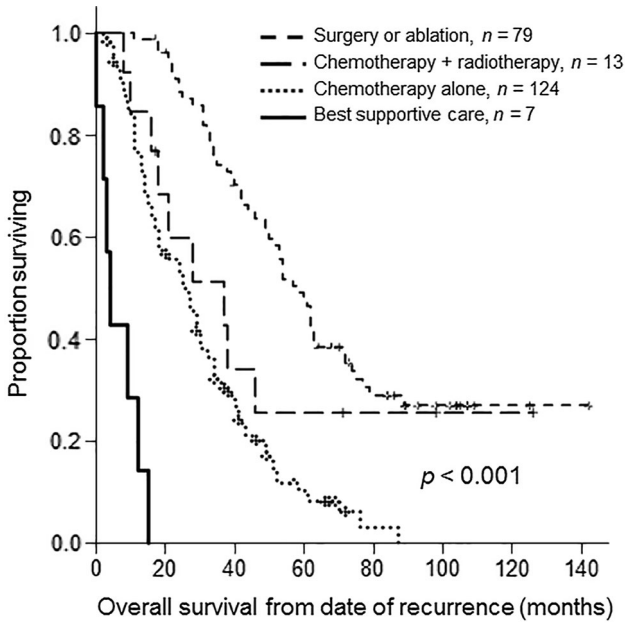

FIG. 2 Overall survival from date of first intrahepatic recurrence, stratified by treatment

resection of adjacent organs, most commonly the diaphragm. These data support resection over ablation as gold-standard treatment for resectable CLM.[19] In carefully selected patients who require parenchymal sparing, CT-guided percutaneous ablation after hepatectomy of metastases < 2 cm is associated with a 0% local tumor progression rate.[20]

Strategies to prevent intrahepatic recurrence include preoperative imaging with MRI and hepatic arterial infusion pump chemotherapy (HAI). Preoperative chemotherapy induces pathological changes in the liver parenchyma, which decrease the sensitivity of CT imaging and intraoperative ultrasound.[21] Prior studies have shown increased sensitivity of MRI over CT to identify hepatic metastases after chemotherapy, particularly with the use of hepatobiliary contrast agents.[13,14,22] Randomized studies have demonstrated that adjuvant HAI increases progression-free and hepatic progression-free survival compared with systemic therapy alone.[23,24]

Treatment of intrahepatic recurrence included repeat hepatectomy or ablation in 79 patients (35%), which was associated with median overall survival of 59 months from date of recurrence. Repeat hepatectomy or ablation was performed in a higher percentage of patients with isolated in situ recurrence (42%) than patients with both de novo and in situ (25%) or isolated de novo recurrence (33%). Prior studies have shown that survival after repeat hepatectomy is comparable to survival after initial resection of CLM.[3,15,25,26] Factors associated with worse survival after repeat hepatectomy include CLM size ≥ 5 cm and R1 resection at initial hepatectomy, and *RAS* mutations.[26,27] These findings suggest that durable survival can be achieved after repeat hepatectomy in selected patients with favorable tumor biology.

A limitation of this study is the lack of a denominator of patients who did not recur after CLM resection. Extensive literature has been published on risk factors for disease relapse after CLM resection, which were not the focus of the present study.[5,25] Another limitation is the absence of data on somatic mutations, because many patients in the study did not undergo mutational testing. *BRAF* and *RAS* mutations have been shown to be important predictors of recurrence and prognosis.[28,29] Furthermore, only 11% of patients underwent preoperative MRI. The small number of patients undergoing preoperative MRI precluded analysis of the differences in true complete response rates with addition of MRI compared with CT alone. Prior studies have shown that the inability to detect liver metastases on MRI imaging is predictive of true complete response.[22,30]

In conclusion, this analysis of intrahepatic recurrence after preoperative chemotherapy and CLM resection demonstrates that both de novo and in situ intrahepatic recurrence predicts significantly worse overall survival than isolated de novo or in situ recurrence. In situ intrahepatic relapse occurred in 53% of patients and resulted from disappearing or missed liver metastases, marginal recurrence, or local tumor progression after ablation. One-third of patients in this series underwent repeat hepatectomy or ablation, which was associated with prolonged survival from date of recurrence.

FUNDING This research was supported in part by the National Institutes of Health through MD Anderson's Cancer Center Support Grant, CA016672.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin.* 2018;68(1):7–30.
2. Abdalla EK, Vauthey JN, Ellis LM, et al. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. *Ann Surg.* 2004;239(6):818–25 (discussion 817–25).
3. Wicherts DA, de Haas RJ, Salloum C, et al. Repeat hepatectomy for recurrent colorectal metastases. *Br J Surg.* 2013;100(6):808–18.
4. D'Angelica M, Kornprat P, Gonen M, et al. Effect on outcome of recurrence patterns after hepatectomy for colorectal metastases. *Ann Surg Oncol.* 2011;18(4):1096–103.
5. Hill CR, Chagpar RB, Callender GG, et al. Recurrence following hepatectomy for metastatic colorectal cancer: development of a model that predicts patterns of recurrence and survival. *Ann Surg Oncol.* 2012;19(1):139–44.
6. Couinaud C. Liver lobes and segments: notes on the anatomical architecture and surgery of the liver. *Presse Med.* 1954;62(33):709–12.

7. Kopetz S, Vauthey JN. Perioperative chemotherapy for resectable hepatic metastases. *Lancet.* 2008;371(9617):963–5.
8. Charnsangavej C, Clary B, Fong Y, Grothey A, Pawlik TM, Choti MA. Selection of patients for resection of hepatic colorectal metastases: expert consensus statement. *Ann Surg Oncol.* 2006;13(10):1261–8.
9. Chun YS, Vauthey JN, Boonsirikamchai P, et al. Association of computed tomography morphologic criteria with pathologic response and survival in patients treated with bevacizumab for colorectal liver metastases. *JAMA.* 2009;302(21):2338–44.
10. Shindoh J, Tzeng CW, Aloia TA, et al. Portal vein embolization improves rate of resection of extensive colorectal liver metastases without worsening survival. *Br J Surg.* 2013;100(13):1777–83.
11. Brouquet A, Abdalla EK, Kopetz S, et al. High survival rate after two-stage resection of advanced colorectal liver metastases: response-based selection and complete resection define outcome. *J Clin Oncol.* 2011;29(8):1083–90.
12. de Jong MC, Pulitano C, Ribero D, et al. Rates and patterns of recurrence following curative intent surgery for colorectal liver metastasis: an international multi-institutional analysis of 1669 patients. *Ann Surg.* 2009;250(3):440–8.
13. Bischof DA, Clary BM, Maithel SK, Pawlik TM. Surgical management of disappearing colorectal liver metastases. *Br J Surg.* 2013;100(11):1414–20.
14. Owen JW, Fowler KJ, Doyle MB, Saad NE, Linehan DC, Chapman WC. Colorectal liver metastases: disappearing lesions in the era of Eovist hepatobiliary magnetic resonance imaging. *HPB (Oxford).* 2016;18(3):296–303.
15. Que FG, Nagorney DM. Resection of 'recurrent' colorectal metastases to the liver. *Br J Surg.* 1994;81(2):255–8.
16. Pawlik TM, Scoggins CR, Zorzi D, et al. Effect of surgical margin status on survival and site of recurrence after hepatic resection for colorectal metastases. *Ann Surg.* 2005;241(5):715–22 (discussion 714–22).
17. Sadot E, Groot Koerkamp B, Leal JN, et al. Resection margin and survival in 2368 patients undergoing hepatic resection for metastatic colorectal cancer: surgical technique or biologic surrogate? *Ann Surg.* 2015;262(3):476–85 (discussion 475–83).
18. Brouquet A, Vauthey JN, Badgwell BD, et al. Hepatectomy for recurrent colorectal liver metastases after radiofrequency ablation. *Br J Surg.* 2011;98(7):1003–9.
19. Chun YS, Vauthey JN. Local therapy for colorectal liver metastases: establishing today's level of evidence and defining tomorrow's roadmap. *J Natl Cancer Inst*. 2017. https://doi.org/10.1093/jnci/djx018.
20. Odisio BC, Yamashita S, Frota L, et al. Planned treatment of advanced metastatic disease with completion ablation after hepatic resection. *J Gastrointest Surg.* 2017;21(4):628–35.
21. Angliviel B, Benoist S, Penna C, et al. Impact of chemotherapy on the accuracy of computed tomography scan for the evaluation of colorectal liver metastases. *Ann Surg Oncol.* 2009;16(5):1247–53.
22. Auer RC, White RR, Kemeny NE, et al. Predictors of a true complete response among disappearing liver metastases from colorectal cancer after chemotherapy. *Cancer.* 2010;116(6):1502–9.
23. Kemeny NE, Gonen M. Hepatic arterial infusion after liver resection. *N Engl J Med.* 2005;352(7):734–5.
24. Kemeny MM, Adak S, Gray B, et al. Combined-modality treatment for resectable metastatic colorectal carcinoma to the liver: surgical resection of hepatic metastases in combination with continuous infusion of chemotherapy—an intergroup study. *J Clin Oncol.* 2002;20(6):1499–505.
25. Hallet J, Sa Cunha A, Adam R, et al. Factors influencing recurrence following initial hepatectomy for colorectal liver metastases. *Br J Surg.* 2016;103(10):1366–76.
26. Andreou A, Brouquet A, Abdalla EK, Aloia TA, Curley SA, Vauthey JN. Repeat hepatectomy for recurrent colorectal liver metastases is associated with a high survival rate. *HPB (Oxford).* 2011;13(11):774–82.
27. Denbo JW, Yamashita S, Passot G, et al. RAS mutation is associated with decreased survival in patients undergoing repeat hepatectomy for colorectal liver metastases. *J Gastrointest Surg.* 2017;21(1):68–77.
28. Margonis GA, Buettner S, Andreatos N, et al. Association of BRAF mutations with survival and recurrence in surgically treated patients with metastatic colorectal liver cancer. *JAMA Surg.* 2018. https://doi.org/10.1001/jamasurg.2018.0996.
29. Kemeny NE, Chou JF, Capanu M, et al. KRAS mutation influences recurrence patterns in patients undergoing hepatic resection of colorectal metastases. *Cancer.* 2014;120(24):3965–71.
30. Park MJ, Hong N, Han K, et al. Use of imaging to predict complete response of colorectal liver metastases after chemotherapy: MR imaging versus CT imaging. *Radiology.* 2017;284(2):423–31.