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Recurrence after partial hepatectomy for metastatic colorectal cancer: The potentially curative role of salvage re-resection

Jean M. Butte, MD[1], **Mithat Gönen, PhD**[2], **Peter J. Allen, MD**[1], **T. Peter Kingham, MD**[1], **Constantinos T. Sofocleous, MD, PhD**[3], **Ronald P. DeMatteo, MD**[1], **Yuman Fong, MD**[1], **Nancy E. Kemeny, MD**[4], **William R. Jarnagin, MD**[1], and **Michael I. D'Angelica, MD**[1]

[1]Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY USA

[2]Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY USA

[3]Department of Radiology, Memorial Sloan Kettering Cancer Center, New York, NY USA

[4]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY USA

Abstract

PURPOSE—Patients with recurrence after complete resection of colorectal liver metastases (CLM) are considered for re-resection as a potential salvage therapy (PST). However, outcomes for this approach are not well defined. We sought to analyze the natural history of recurrence and PST in a large cohort of patients with long-term follow-up.

METHODS—Recurrence patterns, treatments, and outcomes in consecutive patients undergoing resection for CLM were analyzed retrospectively. PST was defined as re-resection of all recurrent disease and effective salvage therapy (EST) as free of disease for 36 months after last PST. Factors associated with PST, EST, and outcomes were analyzed.

RESULTS—Of 952 patients who underwent resection, 594 (62%) recurred (median interval=13 months). Initial recurrences involved liver (n=157,26%), lung (n=167,28%), multiple sites (n=171,29%), and other single sites (n=99,17%). PST was performed in 160/594 (27%), most commonly with a single site of recurrence (n=149). Young age (p=0.01), negative initial resection margin (p=0.003), initial tumor size <5 cm (p=0.006), and recurrence pattern (p<0.001) were independently associated with PST. Thirty-six patients achieved EST (25% of PSTs). Overall median survival was 61 months and 43 months in those that recurred. Median survival of patients undergoing PST was 87 months as compared to 34 months for those who did not.

CONCLUSIONS—Recurrence is common after CLM resection, but 27% of patients were able to undergo PST. Approximately one-quarter of these achieved EST and may be cured. PST is associated with long-term survival and possible cure and therefore active surveillance after CLM resection is justified.

Address correspondence to: Michael I. D'Angelica, MD, Department of Surgery, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, Tel 212-639-3226, Fax 212-717-3218, dangelim@mskcc.org.

Conflicts of Interest: None

Keywords

colorectal metastases; recurrence; salvage therapy; outcomes

INTRODUCTION

Liver is the organ to which colorectal cancer most frequently metastasizes.[1] In 15-25% of colorectal cancer patients, liver metastases are present at initial presentation, and an additional 40-50% will ultimately develop colorectal liver metastases (CLM).[1-4] Hepatic resection is the best treatment for patients with resectable tumors and is associated with long-term survival and cure. Unfortunately, in at least 70% of resected patients, disease will recur.[3, 5, 6] Previous studies on specific patterns of post-hepatectomy recurrence showed that selected patients can undergo complete resection with long-term survival rates better than those reported with palliative treatment.[7, 8] However, these reported outcomes may be related as much to underlying tumor biology and selection bias as to treatment. Importantly, these series have not addressed the complete denominator of patients that have recurred and lack long-term follow-up. However, there are documented cases of cure in patients who have undergone resection of recurrent disease.[9-11] Consequently, in selected patients, complete resection of recurrent disease might be considered a potential salvage therapy (PST).[12-15]

The indications and outcomes for resection of recurrent disease after hepatectomy for CLM have not been well-studied or defined. Resection of recurrence has usually been performed in patients with limited liver or lung-only disease; however, some patients with multiple sites of recurrence have also been re-resected.[16] Improved ablative therapies have broadened treatment options for patients with recurrence.[15, 17] Little is known, however, about the natural history, success rates, and factors predictive of outcome in patients who undergo PST. Previously published studies are mostly small series with limited follow-up that have analyzed re-resection in single-organ sites.[18-21] No prior study has comprehensively reviewed all recurrences after hepatectomy for CLM and the long-term outcomes of recurrence-specific treatments.

The aim of this study was to analyze the natural history of recurrence and PST after complete resection for CLM in a large cohort with long-term follow-up. We also sought to identify factors associated with the performance and outcome of a PST.

METHODS

Subjects and data collection

Following Institutional Review Board approval at Memorial Sloan Kettering Cancer Center (MSKCC), records of all patients who underwent liver resection for CLM between January 1, 1994, and March 31, 2004, were identified from a prospective database. Patients with incomplete information or resection (R2) were excluded. Data were supplemented with retrospective medical record review to document follow-up, patterns and treatment of recurrence, and survival. A clinical risk score (CRS) before liver resection was calculated, as

previously published,[22] for each patient. Scores of 0, 1, or 2 points were classified as "low," and 3, 4, or 5 points as "high."

Selection criteria for the initial liver resection required fitness for a major resection, and an adequate future remnant. Extrahepatic disease was not an absolute contraindication.[23] Preoperative evaluation included physical examination; colonoscopy within the last year; and computed tomography (CT) of chest, abdomen, and pelvis. Magnetic resonance imaging (MRI), and ^{18}F-fluorodeoxyglucose positron emission tomography computed tomography (^{18}FDG PETCT) were utilized selectively. Postoperative follow-up was performed every 4–6 months.

Operative details

The type of initial resection selected was based on the extent of disease and surgical margins. Major hepatectomy was defined as a right or left hemi-hepatectomy, central hepatectomy (Couinaud segments 4, 5, and 8), or extended hepatectomy. Minor hepatectomy was defined as resection of less than a hemi-liver. Hepatic arterial infusion pumps were placed at time of surgery selectively and frequently on prospective trials. An R1 resection was defined as a microscopic margin less than 1 mm.

Follow-up, survival, and recurrence

Surgical mortality was defined as death from postoperative complications within 90 days. At last follow-up, patients were categorized as no evidence of disease (NED), alive with disease (AWD), dead of disease (DOD), dead of other causes (DOC), or dead of unknown causes (DOU). Disease-specific survival (DSS) was defined as the interval between the date of index liver resection or PST (depending on the specific analysis) and the date of last follow-up or death from cancer. Patients who were DOC or DOU were censored. Recurrence-free survival (RFS) was defined as the interval between the date of index liver resection and the date of documented recurrence or last follow-up in patients without recurrence. Recurrences were documented histologically or by definitive radiologic evidence of progression.

Potential salvage therapy and effective salvage therapy

PST was defined as a complete resection of all recurrent disease after initial hepatectomy. Rarely, thermal ablative therapies were used as PST. Treatments considered palliative included chemotherapy, radiation therapy, or incomplete resection. Recurrences and new treatments after a PST were recorded, as were multiple PSTs undertaken in a single patient. Effective salvage therapy (EST) was defined as free of recurrent disease with at least 36 months of follow-up after last PST. Thirty-six months was chosen as the cut-off to define EST since recurrence after this interval is uncommon.[5]

Statistical analysis

Categorical and continuous variables were summarized using proportions, mean (± standard deviation), and median (range). Chi-square and Kruskal-Wallis tests were used to compare categorical and continuous variables, respectively. Univariate and multivariate Cox proportional hazards regression was used to identify factors independently associated with PST. Factors associated with EST were not assessed in multivariate analysis due to

insufficient number of events. All variables significant at the 10% level in univariate analysis were considered for multivariate analysis. P-values from the univariate and multivariate models were from the Wald test. CRS was not included in the multivariate analysis to avoid problems of collinearity with its components included in the analysis. Fifteen of 160 patients undergoing a PST were not included in the EST analysis because they had less than 36 months of follow-up after last PST. Survival curves were constructed by the Kaplan-Meier method and compared using the log-rank test. All tests were two-sided ($p<0.05$). Statistical analysis was performed with S.A.S. (v.9.2) and S.P.S.S (v.19.0).

RESULTS

Clinical presentation

A total of 1,034 patients underwent liver resection for CLM during the study period. Eighty-two (7.9%) patients were excluded, leaving 952 for analysis. Reasons for exclusion were incomplete information (n=48), R2 resection (n=23), or initial liver resection for CLM prior to 1994 (n=11). Tables 1 and 2 summarize clinical and therapeutic characteristics of the primary tumor and CLM for the cohort (N=952).

Five hundred ninety-four (62.4%) patients recurred at a median interval of 13 months (range=1-127). Initial recurrence involved the liver as sole site (n=157,26.4%), the lung as sole site (n=167,28.1%), multiple sites (n=171,28.8%), and other single sites (n=99,16.7%). Other single sites of recurrence were retroperitoneum (n=18), bone (n=17), peritoneum (n=14), pelvis (n=11), colonic anastomosis (n=9), ovaries (n=8), portocaval lymph nodes (n=6), brain (n=5), pancreas (n=2), abdominal wall (n=2), adrenal (n=2), mediastinum (n=2), celiac lymph nodes (n=1), inguinal lymph nodes (n=1), and mesentery (n=1).

Treatment of patients undergoing PST

Of the 594 patients with recurrence, 160 (26.9%) underwent at least one PST and 434 (73.1%) received palliative therapy (Figure 1A). Of these 160 patients, 96 (60.0%) underwent one PST, 46 (28.8%) underwent two, 15 (9.4%) underwent three, and 3 (1.9%) underwent four for subsequent recurrences. One hundred forty-nine (93.1%) of 160 patients who underwent a PST had recurrence at a single site and most (n=94) had a single tumor at the time of initial recurrence. The great majority of patients (156/160, 97.5%) underwent resection as their first PST; R0 resection in 134 and R1 in 22. Of the 156 patients that underwent resection as first PST, 100 received adjuvant chemotherapy, 10 received adjuvant external beam radiation therapy, and 3 underwent thermal ablation for additional tumors. The remaining 4 patients (2.6%) received radiofrequency ablation as their principal PST, 2 of whom received adjuvant chemotherapy.

Uni- and multivariate analyses of factors predictive of PST

Young age, absence of lymphovascular invasion and metastatic lymph nodes from the primary tumor, negative margin of initial liver resection, CEA levels <200 ng/mL, tumor size <5 cm, low CRS, and the pattern of first recurrence were identified on univariate analysis as factors associated with performance of a PST (Table 3). Use of hepatic arterial infusion chemotherapy (HAIC) was not associated with PST. On multivariate analysis,

young age (p=0.01), negative margin of liver resection (p=0.003), tumor size <5 cm (p=0.006), and pattern of recurrence (p<0.001) were independently associated with a PST (Table 3).

Effective salvage therapy

Of the 160 patients who underwent a PST, 15 (9.4%) had less than 36 months of follow-up after their last PST, leaving 145 patients for analysis. Thirty-six of these 145 patients (6.1% of all patients with recurrence after index liver resection and 24.8% of 145 patients undergoing PST) met the criteria for EST. The median follow-up of these 36 patients was 84 months (range=36-172) (Figure 1A). EST was obtained after one PST in 23 (63.9%) patients, two in 8 (22.2%), three in 3 (8.3%), and four in 2 (5.6%). Table 4 summarizes the characteristics of the 145 analyzable PST patients, including the 36 with EST. Negative lymph nodes in the primary (p=0.03), single initial liver metastasis (p=0.03), and low CRS (p=0.03) were significantly associated with EST. Use of HAIC at the time of the index liver resection was not associated with EST. If we limit the analysis to patients without extrahepatic disease or positive margins at their index liver resection (n=647), the EST rate was 7.3% (27/369) of all recurrences and 27.8% (27/97) of those undergoing PST.

Of the 434 patients treated with palliative therapy, 47 (10.8%) were alive at last follow-up. Most of these patients were AWD (n=44) and 3 (0.7%) were NED. Thirty of these 47 patients had at least 3 years of follow-up after last recurrence.

Survival analysis

The median follow-up period was 59 months (range=0-189) for survivors. Median DSS for the cohort (N=952) was 61 months (95% CI, 54.8-67.2), with actuarial DSS of 50.1% at 5 years. Median RFS of the cohort was 21 months (95% CI, 18.5-23.5), with actuarial RFS of 31.9% at 5 years.

Median DSS of those patients who recurred (n=594) was 43 months (95% CI, 39.6-46.4), with actuarial DSS of 31.3% at 5 years. Median DSS, measured from date of initial liver resection, was 87 months (95% CI, 59.6-114.4) in patients who underwent a PST (n=160) and 34 months (95% CI, 31-37) in patients who received palliative treatment (n=434). The actuarial 5-year DSS was 65.4% for patients undergoing PST and 19% for palliative treatment (Figure 1B).

DISCUSSION

The treatment of choice for patients with resectable CLM is complete resection[2] because it is associated with long-term survival and cure.[10] Nevertheless, the majority of patients will develop recurrence, most commonly involving liver and/or lungs.[5] Resection as PST has not been well studied. Previous publications suggest that resection of recurrent disease in selected patients is as safe and effective as the initial operation in terms of survival and postoperative complications.[16] However, the denominator from which patients are chosen for re-resection is typically ill-defined and long-term outcomes poorly documented.[18, 24, 25] Also, previous analyses are limited by small cohorts and short follow-up, and lack definition

of the complete denominator of patients with recurrence. Additionally, most studies evaluate treatment of the first recurrence or limit their analyses to single organ sites.[19, 26, 27]

de Jong et al[6] evaluated curative intent surgery for liver recurrence in a multicenter study. Six hundred forty-five of 1706 patients presented with liver recurrence and re-resection was performed in 38%. However, the analysis did not include patients with extrahepatic recurrence. A similar study by Jones et al[28] analyzed surgical treatment of liver recurrence in 150 patients. Survival was significantly better in patients who underwent complete resection than those treated without resection. However, this analysis did not include the 65 patients who presented with extrahepatic recurrence and had short follow-up time (19 months).

The present study differs from previous studies in several aspects. It includes a complete assessment of all types of recurrences and provides long-term follow-up to evaluate the durability of a PST. This is the first study that comprehensively defines long-term survival and possible cure after a PST in post-hepatectomy patients with recurrent CLM. Since most patients develop recurrence within 24 months, EST was defined as free of recurrent disease with at least 36 months of follow-up after last PST. While some patients NED at 36 months might ultimately fail, the great majority are likely cured of their disease. We also described the outcomes of patients not selected for a PST, demonstrating their relatively poor survival. These results help to understand the natural history of this clinical scenario and provide definitions of PST and EST. Also, this information can be used to guide further studies and develop guidelines for follow-up and treatment.

This study confirmed that at least 60% of patients with CLM will recur after complete resection. The minority selected for PST presented with a single recurrent tumor in a single organ. The majority of patients received palliative systemic chemotherapy or supportive treatment for their recurrence. In comparison with patients who were able to undergo PST, those who received palliative therapy had a shorter survival. Palliative systemic chemotherapy was rarely associated with cure; only 3 patients were NED at last follow-up.

Prognostic factors such as number and size of liver metastases, lymph node status of the primary tumor, CEA level, presence of extrahepatic disease, and margin-negative resection have been associated with survival after hepatic resection for CLM. However, these factors have not been shown to predict possibility of a PST after recurrence. This study showed that young age, margin-negative liver resection, tumor size <5 cm, and pattern of recurrence were associated with PST.[5, 29] The CRS was excluded from the multivariate analysis because its components were individually included.

This study also evaluated patients who achieved long-term DFS after PST (EST). It is important that 1 in 4 patients who underwent a PST were definitively salvaged and may be cured of their disease. Unfortunately, it is a small minority (6.06%) of all patients with recurrence that achieve EST. Nonetheless, we find this rate along with the associated long-term survival among patients undergoing PST sufficient to justify active surveillance since the outcome of these patients may include cure. This study also identified the CRS and the margin of the initial liver resection as factors associated with EST, factors that may be

helpful prognostic indicators. Due to limited events, these factors could not be analyzed in a multivariate analysis.

This study, as with all retrospective studies, has limitations that should temper interpretation of the results. Intrinsic to the nature of the data used in this retrospective analysis is that the choice to proceed with a PST was not mandated by a specific protocol. Many factors may have gone into the decision to proceed with PST, introducing bias into the results. Nonetheless, all our patients were under active surveillance and PST was considered in the great majority of situations.

In summary, this is the first study that evaluates re-resection, including all recurrences and their treatments, as a PST for recurrence following initial complete resection of CLM. The results demonstrate that 26.9% of patients were amenable to a PST after recurrence and that 6.06% of all patients with recurrence and 25% of patients who underwent PST may be cured by re-resection. Active follow-up is recommended to select patients who may be amenable to PST.

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Salvage surgery for recurrence after hepatic resection for metastatic colorectal cancer has not been well-studied. In this study, 27% of patients underwent salvage surgery, which was associated with prolonged survival and cure. Active surveillance after initial hepatic resection is justified.

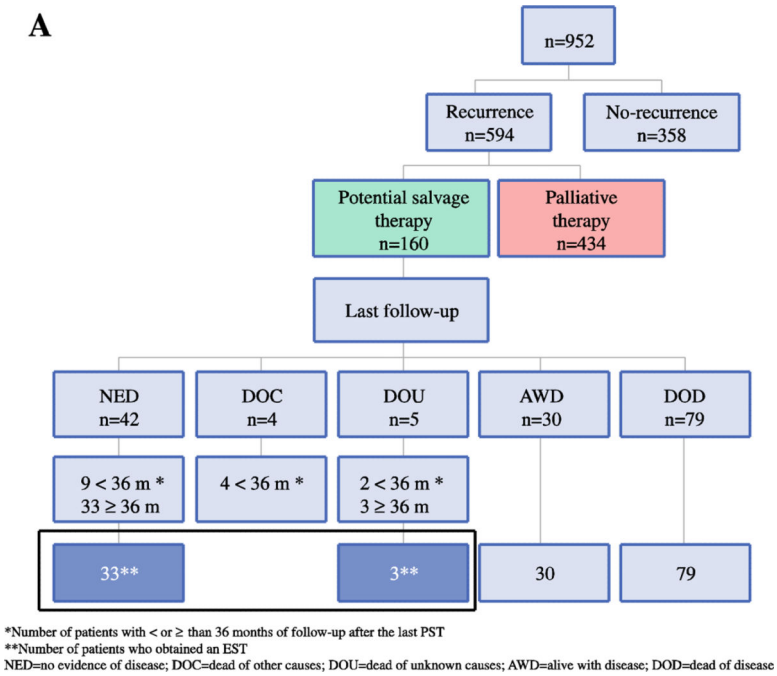

Figure 1A.

Natural history of patients with CLM who underwent complete resection, presented with recurrence, and received a PST.

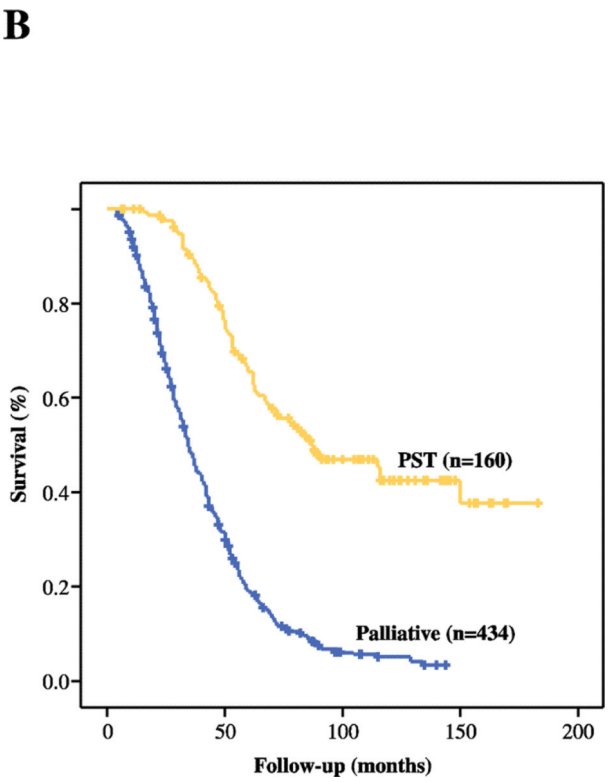

Figure 1B.
Disease-specific survival of patients treated with a PST (n=160) and those who underwent a palliative treatment (n=434).

Table 1

Clinical characteristics of 952 patients undergoing complete resection for CLM

	Total N=952
Gender	
Male	544 (57.1)
Female	408 (42.9)
Age	
Median (range)	62.5 (23-89)
Mean ± SD	61.1 ± 12
Simultaneous diagnosis	
No	827 (86.9)
Yes	125 (13.1)
Disease-free interval < 12 months	
No	507 (53.3)
Yes	445 (46.7)
Disease-free interval [months]	
Median (range)	(13 (0-307)
Mean ± SD	18.6 ± 24
PRIMARY TUMOR	
Primary	
Colon	689 (72.4)
Rectum	263 (27.6)
T (n=887)	
1	28 (3.2)
2	119 (13.4)
3	693 (78.1)
4	47 (5.3)
Differentiation (n=848)	
Well	25 (2.9)
Moderately	740 (87.3)
Poorly	83 (9.8)
LVI (n=643)	
No	396 (61.6)
Yes	247 (38.4)
PNI (n=556)	
No	444 (79.9)
Yes	112 (20.1)

	Total N=952
Lymph node status	
Negative	371 (39.0)
Positive	581 (61.0)
Total number of lymph nodes resected (n=809)	
Median (range)	11 (0-62)
Mean ± SD	13 ± 9.2
Total positive number (n=883)	
Median (range)	1 (0-38)
Mean ± SD	2.19 ± 3.3

CLM=colorectal liver metastases, SD=standard deviation, LVI=lymphovascular invasion, PNI=perineural invasion.

Table 2

Clinical and therapeutic characteristics of liver metastases in 952 patients undergoing complete liver resection for colorectal liver metastases

LIVER METASTASES	Total N=952
Extrahepatic disease	
No	794 (83.4)
Yes	158 (16.6)
Major Resection	
No	371 (39.0)
Yes	581 (61.0)
Margin	
Negative	808 (84.9)
Positive	144 (15.1)
CEA > 200 ng/mL (n=850)	
No	755 (88.8)
Yes	95 (11.2)
Preoperative CEA ng/mL (n=847)	
Median (range)	15 (0-16348)
Mean ± SD	154 ± 868
>1 tumor	
No	438 (46.0)
Yes	514 (54.0)
Number of tumors	
Median (range)	2 (1-17)
Mean ± SD	2.6 ± 2.4
Tumor size > 5 cm	
No	637 (66.9)
Yes	315 (33.1)
Tumor size (largest) [cm]	
Median (range)	4 (0-40)
Mean ± SD	4.9 ± 3.4
Clinical risk score	
0	59 (6.2)
1	259 (27.2)
2	316 (33.2)
3	230 (24.2)
4	71 (7.5)

LIVER METASTASES	**Total N=952**
5	17 (1.8)
Clinical risk score	
Low	634 (66.6)
High	318 (33.4)
PERIOPERATIVE TREATMENTS	
Neoadjuvant chemotherapy (n=936)	
No	709 (75.7)
Yes	227 (24.3)
Adjuvant chemotherapy (n=893)	
No	124 (13.9)
Yes	769 (86.1)
HAIP chemotherapy (n=929)	
No	676 (72.8)
Yes	253 (27.2)

CEA=carcinoembryonic antigen, SD=standard deviation, HAIP=hepatic arterial infusion pump.

Table 3

Uni- and multivariate analysis of factors associated with the performance of a potential salvage therapy

	Total n=594	PST YES n=160 (%)	PST NO n=434 (%)	P Univariate	Multivariate	Odds ratio (95% CI)
Gender				0.1		
Male	337	99 (29.4)	238 (70.6)			
Female	257	61 (23.7)	196 (76.3)			
Age				0.009	0.01	1.02 (1.00-1.05)
Median (range)	62 (23-89)	59 (31-81)	62.5 (23-89)			
Mean ± SD	60.2 ± 11.9	58.1 ± 10.9	61 ± 12.2			
Simultaneous diagnosis				0.2		
No	505	131 (25.9)	374 (74.1)			
Yes	89	29 (32.6)	60 (67.4)			
Disease-free interval <12 months				0.6		
No	296	77 (26.0)	219 (74.0)			
Yes	298	83 (27.9)	215 (72.1)			
Disease-free interval [months]				0.8		
Median (range)	11 (0-307)	10 (0-151)	12 (0-307)			
Mean ± SD	17.3 ± 24	16.9 ± 22.4	17.5 ± 24.6			
PRIMARY TUMOR						
Primary				0.4		
Colon	425	111 (26.1)	314 (73.9)			
Rectum	169	49 (29.0)	120 (71.0)			
T (n=563)				0.3		
1	16	5 (31.2)	11 (68.8)			
2	65	13 (20.0)	52 (80.0)			
3	448	127 (28.3)	321 (71.7)			
4	34	6 (17.6)	28 (82.4)			
Differentiation (n=543)				0.8		
Well	17	5 (29.4)	12 (70.6)			
Moderately	474	129 (27.2)	345 (72.8)			
Poorly	52	12 (23.1)	40 (76.9)			
LVI (n=394)				0.03		
No	222	75 (33.8)	147 (66.2)			
Yes	172	41 (23.8)	131 (76.2)			
PNI (n=342)				0.6		
No	256	75 (29.3)	181 (70.7)			

	Total n=594	PST YES n=160 (%)	PST NO n=434 (%)	P Univariate	Multivariate	Odds ratio (95% CI)
Yes	86	22 (25.6)	64 (74.4)			
Lymph node status				0.009		
Negative	216	72 (33.3)	144 (66.7)			
Positive	378	88 (23.3)	290 (76.7)			
Total number of lymph nodes resected (n=518)				0.2		
Median (range)	11 (0-62)	12 (0-52)	11 (0-62)			
Mean ± SD	13.3 ± 9.3	14.2 ± 10	13 ± 8.9			
Total positive number (n=558)				0.034		
Median (range)	1 (0-38)	1 (0-14)	1 (0-38)			
Mean ± SD	2.5 ± 3.5	1.9 ± 2.8	2.7 ± 3.7			
LIVER METASTASES						
Extrahepatic disease				1		
No	454 (76.4)	131 (28.9)	323 (71.1)			
Yes	140 (23.6)	29 (20.7)	111 (79.3)			
Major Resection				0.1		
No	217	66 (30.4)	151 (69.6)			
Yes	377	94 (24.9)	283 (75.1)			
Margin				0.001	0.003	
Negative	485	144 (29.7)	341 (70.3)			4.13 (1.6-10.6)
Positive	109	16 (14.7)	93 (85.3)			1
CEA < 200 ng/mL (n=542)				0.001		
No	78	10 (12.8)	68 (87.2)			
Yes	464	138 (29.7)	326 (70.3)			
Preoperative CEA ng/mL (n=538)				0.5		
Median (range)	16.4 (0-16348	10 (0.5-16348)	24.9 (0-6870)			
Mean ± SD	203 ± 1048	253 ± 1689	183 ± 660			
>1 tumor				0.7		
No	237	66 (27.8)	171 (72.2)			
Yes	357	94 (26.3)	263 (73.7)			
Number of tumors				0.1		
Median (range)	2 (1-17)	2 (1-11)	2 (1-17)			
Mean ± SD	2.9 ± 2.7	2.6 ± 2.4	3 ± 2.7			
Tumor size < 5 cm				0.001	0.006	
No	209	39 (18.7)	170 (81.3)			2.42 (1.27-4.59)

	Total n=594	PST YES n=160 (%)	PST NO n=434 (%)	P Univariate	Multivariate	Odds ratio (95% CI)
Yes	385	121 (31.4)	264 (68.6)			1
Tumor size (largest) [cm]				0.002		
Median (range)	4.2 (0.6-40)	3.5 (0.6-15)	4.5 (0.7-40)			
Mean ± SD	5 ± 3.6	4.3 ± 2.8	5.3 ± 3.8			
Clinical risk score				0.003		N/A
0	33	15 (45.5)	18 (54.5)			
1	131	35 (26.7)	96 (73.3)			
2	189	60 (31.7)	129 (68.3)			
3	168	41 (24.4)	127 (75.6)			
4	58	9 (15.5)	49 (84.5)			
5	15	0	15 (100.0)			
Clinical risk score				0.006		
Low	353	110 (31.2)	243 (68.8)			
High	241	50 (20.7)	191 (79.3)			
Neoadjuvant chemotherapy (n=590)				0.8		
No	420	112 (26.7)	308 (73.3)			
Yes	170	47 (27.6)	123 (72.4)			
Adjuvant chemotherapy (n=569)				0.06		
No	57	22 (38.6)	35 (61.4)			
Yes	512	133 (26.0)	379 (64.0)			
HAIP chemotherapy (n=586)				0.9		
No	419	113 (27.0)	306 (73.0)			
Yes	167	46 (27.5)	121 (72.5)			
Pattern of first recurrence				<0.0001	<0.001	
Lung only recurrence	167	70 (41.9)	97 (58.1)			10.8 (4.1-28.3)
Liver only recurrence	157	49 (31.2)	108 (68.8)			8.6 (3.2-22.9)
Other single sites only recurrence	99	12 (12.1)	87 (87.9)			5.5 (1.9-15.5)
Multiple sites recurrence	171	29 (17.0)	142 (83.0)			1

* Results of the multivariate analysis shown only for significant variables. The probability of getting a PST decreased as the age increased. Clinical risk score was not included in the multivariate analysis to avoid problems of collinearity with their components that were included in the analysis. PST=potential salvage therapy, SD=standard deviation, LVI=lymphovascular invasion, PNI=perineural invasion, CEA=carcinoembryonic antigen, HAIP=hepatic arterial infusion pump.

Table 4

Comparison of clinical and therapeutic features between patients who obtained and did not obtain effective salvage therapy after potential salvage therapy

	Total 145	EST YES n=36 (%)	EST NO n=109 (%)	p Univariate
Gender				0.3
Male	91	20 (22.0)	71 (78.0)	
Female	54	16 (29.6)	38 (70.4)	
Age				0.9
Median (range)	59 (31-81)	61.5 (31-81)	59 (37-78)	
Mean ± SD	58.4 ± 10.7	58.3 ± 14.2	58.4 ± 9.4	
Simultaneous diagnosis				0.6
No	119	31 (26.1)	88 (73.9)	
Yes	26	5 (19.2)	21 (80.8)	
Disease-free interval < 12 months				0.7
No	71	19 (26.8)	52 (73.2)	
Yes	74	17 (23.0)	57 (77.0)	
Disease-free interval [months]				0.7
Median (range)	10 (0-151)	13 (0-128)	9 (0-151)	
Mean ± SD	17.4 ± 23.3	18.6 ± 24.5	17 ± 22	
PRIMARY TUMOR				
Primary				0.5
Colon	99	23 (23.2)	76 (76.8)	
Rectum	46	13 (28.3)	33 (71.7)	
T (n=138)				0.8
1	4	1 (25.0)	3 (75.0)	
2	12	2 (16.7)	10 (83.3)	
3	116	31 (26.7)	85 (73.3)	
4	6	1 (16.7)	5 (83.3)	
Differentiation (n=135)				0.9
Well	3	1 (33.3)	2 (66.7)	
Moderately	122	31 (25.4)	91 (74.6)	
Poorly	10	2 (20.0)	8 (80.0)	
LVI (n=107)				0.8
No	70	18 (25.7)	52 (74.3)	
Yes	37	8 (21.6)	29 (78.4)	
PNI (n=89)				1
No	69	19 (27.5)	50 (72.5)	

	Total 145	EST YES n=36 (%)	EST NO n=109 (%)	p Univariate
Yes	20	5 (25.0)	15 (75.0)	
Lymph nodes (primary)				0.03
Negative	66	22 (33.3)	44 (66.7)	
Positive	79	14 (17.7)	65 (82.3)	
Total number of lymph nodes resected (n=122)				0.6
Median (range)	12 (0-52)	10 (0-39)	12 (0-52)	
Mean ± SD	14.5 ± 10.5	13.7 ± 10.4	14.7 ± 10.6	
Total positive number (n=138)				0.4
Median (range)	1 (0-14)	0 (0-12)	1 (0-14)	
Mean ± SD	2 ± 2.9	1.7 ± 3.3	2.1 ± 2.7	
LIVER METASTASES				
Extrahepatic disease				0.8
No	106	27 (25.5)	79 (74.5)	
Yes	39	9 (23.1)	30 (76.9)	
Major Resection				1
No	57	14 (24.6)	43 (75.4)	
Yes	88	22 (25.0)	66 (75.0)	
Margin				0.3
Negative	133	35 (26.3)	98 (73.7)	
Positive	12	1 (8.3)	11 (91.7)	
CEA > 200 ng/mL (n=134)				0.7
No	125	31 (24.8)	94 (75.2)	
Yes	9	1 (111)	8 (88.9)	
Preoperative CEA ng/mL (n=134)				0.6
Median (range)	10.2 (0.5-16348)	10.2 (0.5-12325)	10.3 (0.5-16348)	
Mean ± SD	275 ± 1774	403 ± 2176	235 ± 1639	
>1 tumor				0.03
No	57	20 (35.1)	37 (64.9)	
Yes	88	16 (18.2)	72 (81.8)	
Number of tumors				0.1
Median (range)	2 (1-11)	1 (1-11)	2 (1-11)	
Mean ± SD	2.8 ± 2.5	2.3 ± 2.1	2.9 ± 2.6	
Tumor size > 5cm				0.5
No	109	29 (26.6)	80 (73.4)	
Yes	36	7 (19.4)	29 (80.6)	

	Total 145	EST YES n=36 (%)	EST NO n=109 (%)	p Univariate
Tumor size (largest) [cm]				0.1
Median (range)	3.5 (0.6-14.5)	3.1 (1.2-9.5)	4 (0.6-14.5)	
Mean ± SD	4.3 ± 2.7	3.7 ± 2.2	4.4 ± 2.9	
Clinical risk score				0.03
0	13	7 (53.8)	6 (46.2)	
1	32	11 (34.4)	21 (65.6)	
2	54	11 (20.4)	43 (79.6)	
3	38	6 (15.8)	32 (84.2)	
4	8	1 (12.5)	7 (87.5)	
5	0	0	0	
Clinical risk score				0.09
Low	99	29 (29.3)	70 (70.7)	
High	46	7 (15.2)	39 (84.8)	
Neoadjuvant chemotherapy (n=144)				0.7
No	100	24 (24.0)	76 (76.0)	
Yes	44	12 (27.3)	32 (72.7)	
Adjuvant chemotherapy (n=140)				0.8
No	17	3 (17.6)	14 (82.4)	
Yes	123	31 (25.2)	92 (74.8)	
HAIP chemotherapy (n=144)				0.8
No	102	25 (24.5)	77 (75.5)	
Yes	42	11(26.2)	31 (73.8)	
Pattern of first recurrence				0.8
Liver only recurrence	44	10 (22.7)	34 (77.3)	
Lung only recurrence	64	18 (28.1)	46 (71.9)	
Other single sites only recurrence	26	6 (23.1)	20 (76.9)	
Multiple sites recurrence	11	2 (18.2)	9 (81.8)	
Number of tumors after recurrence				0.78
Solitary	85	26 (30.6)	59 (69.4)	
Multiple	60	10 (16.7)	50 (83.3)	
Type of resection after 1st recurrence (n=141)				0.026
R0 resection	121	34 (28.1)	87 (71.9)	
R1 resection	20	1 (5.0)	19 (95.0)	

EST=effective salvage therapy, SD=standard deviation, LVI=lymphovascular invasion, PNI=perineural invasion, CEA=carcinoembryonic antigen, HAIP=hepatic arterial infusion pump.