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Margin Status Remains an Important Determinant of Survival after Surgical Resection of Colorectal Liver Metastases in the Era of Modern Chemotherapy

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Abstract

Objective—To determine the impact of surgical margin status on overall survival (OS) of patients undergoing hepatectomy for colorectal liver metastases (CLM) after modern preoperative chemotherapy.

Summary Background Data—In the era of effective chemotherapy for CLM, the association between surgical margin status and survival has become controversial.

Methods—Clinicopathologic data and outcomes for 378 patients treated with modern preoperative chemotherapy and hepatectomy were analyzed. The effect of positive margins on OS was analyzed in relation to pathologic and computed tomography-based morphologic response to chemotherapy.

Results—Fifty-two of 378 resections (14%) were R1 resections (tumor-free margin < 1 mm). The 5-year OS rates for patients with R0 resection (margin ≥ 1 mm) and R1 resection were 55% and 26%, respectively (P=0.017). Multivariate analysis identified R1 resection (P=0.03) and minor pathologic response to chemotherapy (P=0.002) as the 2 factors independently associated with worse survival. The survival benefit associated with negative margins (R0 vs. R1 resection) was greater in patients with suboptimal morphologic response (5-year OS rate: 62% vs. 11%, P=0.007) than in patients with optimal response (3-year OS rate: 92% vs. 88%, P=0.917) and greater in patients with minor pathologic response (5-year OS rate: 46% vs. 0%, P=0.002) than in patients with major response (5-year OS rate: 63% vs. 67%, P=0.587).

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Conflicts of Interest

The authors report no conflicts of interest relevant to this article.

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Conclusions—In the era of modern chemotherapy, negative margins remain an important determinant of survival and should be the primary goal of surgical therapy. The impact of positive margins is most pronounced in patients with suboptimal response to systemic therapy.

INTRODUCTION

Hepatic resection represents the basis for curative treatment of colorectal liver metastases (CLM), resulting in 5-year survival rates as high as 58% in selected patients.[1] Recent improvements in survival after resection of CLM are due to multiple factors.[2] Advances in operative techniques and strategies (i.e., portal vein embolization and staged hepatectomy), as well as surgical selection criteria based less on conventional clinicopathologic factors and more on the ability to clear disease while leaving behind an adequate future liver remnant, have contributed to an increasing number of patients being offered resection with curative intent.[3–5] Importantly, these advances have been paralleled by the development of highly effective chemotherapeutic and biologic agents for patients with metastatic colorectal cancer.[6–10]

Contemporary systemic therapy for patients with CLM typically includes either oxaliplatin- or irinotecan-containing regimens, often combined with targeted agents such as bevacizumab or cetuximab. Preoperative administration of such systemic therapy in patients with CLM has been shown to result in high response rates and increased rates of resectability.[7–9] Recent investigations have also demonstrated that response to preoperative chemotherapy as assessed by histologic evaluation of the surgical specimen after resection of CLM is a valuable predictor of survival in patients with CLM.[11, 12] In addition, we recently found that chemotherapy-induced morphologic changes detected on preoperative computed tomography (CT) correlated with both pathologic response and survival and appeared to represent a useful clinical surrogate for disease biology.[13]

Traditionally, one of the criteria used to select patients for hepatectomy for CLM has been the predicted ability to achieve pathologically negative surgical margins. This paradigm is supported by several studies demonstrating that so-called R1 resection (tumor-free margin < 1 mm) is associated with worse overall survival than R0 resection (tumor-free margin ≥ 1 mm).[14–18] However, other studies have found that R1 resection does not achieve independent significance as a predictor of survival in multivariate analysis.[15, 19, 20] These include a study published in 2008 that found similar 5-year overall survival rates following R0 and R1 resection (61% and 57%, respectively) among 436 patients treated with perioperative chemotherapy and an aggressive surgical approach.[19] These conflicting findings regarding the impact of positive margins raise the question of whether R1 resection negatively impacts survival because of the adverse effect of microscopic residual tumor left behind at the time of surgery or rather reflects a more aggressive tumor phenotype that makes complete resection with histologically negative margins harder to achieve. That question is difficult to answer on the basis of results of prior studies given the heterogeneity of the patients and treatment modalities in those studies.

The objective of the current study was to better understand the impact of surgical margin status on overall survival after surgical resection of CLM while accounting for tumor biology as assessed by response to preoperative chemotherapy. To do this, we analyzed a homogeneous group of patients with CLM who had been treated with modern chemotherapeutic agents followed by hepatic resection. Response to systemic therapy was evaluated according to previously established CT-based morphologic and pathologic criteria.

METHODS

Patient Inclusion Criteria

The prospectively maintained hepatobiliary surgical database at The University of Texas MD Anderson Cancer Center was queried to identify all consecutive patients with CLM treated with preoperative chemotherapy and subsequent hepatectomy with curative intent between September 1997 and January 2010. Patients treated with concomitant radiofrequency ablation were excluded. Patients with extrahepatic metastases were also excluded from the study. Clinicopathologic data (described in detail under Statistical Analysis below) were extracted from the patients' medical records. Institutional Review Board approval was obtained prior to data retrieval and analysis.

Preoperative Assessment

Preoperative assessment included a medical history, physical examination, laboratory evaluation, and imaging studies. Helical CT with liver protocol or magnetic resonance imaging was used to define the extent and location of CLM. Beginning in 1998, fluorodeoxyglucose positron emission tomography was selectively used to rule out extensive extrahepatic disease and to confirm the metastatic nature of atypical lesions.[21]

Imaging studies were reviewed by an experienced hepatobiliary radiologist, and our previously described CT-related morphologic criteria were used to assess morphologic response to preoperative chemotherapy.[13] In brief, CLM response was classified in group 3 if there was heterogeneous attenuation and a thick, poorly defined tumor-liver interface; in group 1 if there was homogeneous low attenuation and a thin, sharply defined tumor-liver interface; and in group 2 if there were mixed characteristics. Morphologic response to preoperative chemotherapy was defined as optimal if CLM changed from group 3 or 2 to group 1. Morphologic response was defined as suboptimal if CLM changed from group 3 to group 2, remained in the same category, or changed to a higher-numbered group. In patients with multiple CLM, morphologic response was scored on the basis of the response seen in the majority of lesions.

Treatment plans were made during case presentations at a multidisciplinary liver tumor conference attended by hepatobiliary surgeons, diagnostic radiologists, interventional radiologists, and medical oncologists. Decision-making was based on the location and extent of CLM, the presence of extrahepatic disease, and radiographic response to preoperative chemotherapy. Hepatectomy was considered in patients with CT volumetry indicating that all CLM could be safely resected with preservation of a sufficient future liver remnant. In patients with an anticipated insufficient future liver remnant volume, preoperative portal vein embolization was used to induce hypertrophy of the future liver remnant.[22]

Surgical Procedure

During laparotomy, the peritoneal cavity was inspected to rule out previously unrecognized extrahepatic disease. Intraoperative ultrasonography of the liver was performed in each case to confirm and to better define the location of CLM and their relation to portal pedicles and hepatic veins. Parenchymal transection was performed under total or selective hepatic inflow vascular exclusion using the cavitron ultrasonic surgical aspirator (CUSA, Valleylab, Boulder, CO), and hemostasis was achieved using saline-linked cautery (dissecting sealer DS 3.0, Tissuelink Medical, Inc., Dover, NH).[23] For this study, major hepatectomy was defined as resection of 3 or more contiguous liver segments according to Couinaud's classification.[24]

Postoperative Evaluation

Postoperative mortality was defined as any death within 90 days following resection, and postoperative morbidity was defined as any complication within the same time period. Postoperative complications were graded according to a standard classification system.[25] Major complications were classified as complications requiring surgical, endoscopic, or radiologic intervention (grade III); life-threatening complications requiring intensive-care management (grade IV); and death (grade V). Postoperative liver insufficiency was defined as a postoperative peak bilirubin level > 7 mg/dL.[26]

All specimens were subjected to histologic evaluation to confirm the diagnosis of metastatic colorectal cancer, the degree of pathologic response to preoperative chemotherapy, and the width of the tumor-cell-free surgical margin. Margin width was determined prospectively using the shortest distance from the edge of the tumor to the line of parenchymal transection. R1 resection was defined as the presence of tumor cells within the space up to 1 mm from the transection line, whereas R0 resection was defined as complete tumor resection with no tumor cells within 1 mm of the transection line.[15] Pathologic response to preoperative chemotherapy was graded as previously described,[12] with the area of residual viable tumor cells within each metastatic lesion estimated as a percentage of the total tumor surface area. CLM with 0–49% residual viable tumor cells were considered to have a major pathologic response, while CLM with ≥ 50% residual viable tumor cells were considered to have a minor pathologic response. In patients with multiple tumor nodules, the mean of the values for the various nodules was used to define overall pathologic response.

Statistical Analysis

Quantitative and qualitative variables were summarized in terms of median (range), mean (standard deviation), and frequency (percentage). Comparisons between groups were analyzed with the chi-square or Fisher exact test for categorical variables and the Mann-Whitney *U* test for continuous variables, as appropriate. Patients were stratified by pathologic response to preoperative chemotherapy, and the clinicopathologic characteristics of patients who had a major pathologic response were compared with the clinicopathologic characteristics of patients who had a minor response. Overall survival rates were calculated from the date of resection to the date of death or last follow-up using the Kaplan-Meier method and compared using log-rank tests. The effect of R1 resection on overall survival was analyzed in the entire patient cohort as well as in subgroups of patients stratified by pathologic and morphologic response to preoperative chemotherapy.

To identify risk factors associated with overall survival in groups of patients treated with preoperative chemotherapy and subsequent hepatectomy for CLM, we evaluated the following clinicopathologic variables in univariate analysis: sex (male versus female), age (≥ 60 versus < 60 years), body mass index (> 30 versus ≤ 30 kg/m^2), timing of detection of CLM (synchronous versus metachronous), location of the primary tumor (rectum versus colon), status of the regional lymph nodes for the primary tumor (positive versus negative), preoperative chemotherapy for CLM (irinotecan versus oxaliplatin), preoperative systemic therapy with bevacizumab (administered versus not), preoperative systemic therapy with cetuximab (administered versus not), number of cycles of preoperative chemotherapy (≥ 6 versus < 6), pathologic response to preoperative chemotherapy (major versus minor), 2-stage hepatectomy (performed versus not), portal vein embolization (performed versus not), associated procedure (performed versus not), major hepatectomy (performed versus not), major postoperative complication (yes versus no), blood transfusion required (yes versus no), estimated blood loss (> 1000 mL versus ≤ 1000 mL), number of CLM (multiple versus solitary), diameter of the largest of the CLM (≥ 3 versus < 3 cm), carcinoembryonic antigen (CEA) level (≥ 10 ng/mL versus < 10 ng/mL), status of the resection margins on

microscopic analysis (R1 versus R0), and postoperative chemotherapy for CLM (administered versus not).

All variables associated with survival with $P \leq 0.1$ in the univariate proportional hazards models were subsequently entered into a Cox multivariate regression model with backward elimination. P values ≤ 0.05 were considered statistically significant. Statistical analyses were performed using the SPSS software package, version 19.2 (SPSS, Chicago, IL).

RESULTS

Patient Characteristics

Among 494 consecutive patients who underwent hepatectomy for CLM after preoperative chemotherapy during the study period, 116 patients were treated with concomitant radiofrequency ablation and were excluded from the study. The clinicopathologic data of the remaining 378 patients are summarized in Table 1. The median age was 58 years (range, 25–85 years), and 56% of the patients were male. The median number of CLM was 2 (range, 1–75), and 49% of patients had CLM with largest diameter ≥ 3 cm. Preoperative chemotherapy regimens included oxaliplatin in 62% of patients and irinotecan in 38% of patients, and the median number of cycles was 6 (range, 2–36). Bevacizumab and cetuximab were used in combination with chemotherapy in 61% and 6% of the patients, respectively. Postoperative chemotherapy was offered to medically fit patients with the intention of completing a combined preoperative plus postoperative total of 6 months of systemic treatment. A total of 217 patients (57%) had a major pathologic response to preoperative chemotherapy, while 161 patients (43%) had a minor pathologic response.

The majority of the patients (259/378, 69%) underwent major hepatectomy, including 104 (28%) who underwent extended hepatectomy. Thirty patients (8%) underwent staged hepatectomy, consisting of a limited resection of CLM located in the left liver followed by right (± segment 4) portal vein embolization and subsequent right (or extended right) hepatectomy, to achieve complete tumor resection. At histologic evaluation, 52 patients (14%) had an R1 resection, while 326 patients (86%) had an R0 resection. Postoperative chemotherapy for CLM was administered to 260 patients (69%), including 71% of patients with minor pathologic response to preoperative therapy and 67% with major pathologic response. In patients with minor pathologic response to preoperative chemotherapy, the postoperative chemotherapy regimen was either enriched with bevacizumab or cetuximab (depending on prior exposure and k-ras mutation status), or the entire regimen was changed to a second line of modern chemotherapy.

Morphologic response to preoperative chemotherapy was evaluable for 202 of the 378 patients studied. In the remaining176 patients, morphologic response could not be assessed because of small tumor size, lack of high-quality prechemotherapy CT imaging, or the use of magnetic resonance imaging as the preoperative imaging modality. Sixty-five patients (32%) had an optimal morphologic response, and 137 patients (68%) had a suboptimal morphologic response.

Patient Characteristics by Response to Preoperative Chemotherapy

Patient characteristics by pathologic response to preoperative chemotherapy (major or minor) are summarized in Table 1. Synchronous presentation of CLM was more frequent in patients with a major pathologic response (70%) than in patients with a minor response (59%) ($P = 0.033$). The median diameter of the largest of the CLM was larger in patients with a minor pathologic response (3 [1–18] cm) than in patient with a major response (2 [1–16] cm) ($P < 0.0001$). Although within the normal range, the median preoperative CEA level was higher in patients with a minor pathologic response (5 [1–1392] ng/mL) than in patients

with a major response (2 [0–727] ng/mL) ($P < 0.0001$). Fewer patients with a major pathologic response than patients with a minor response required perioperative blood transfusion (14% versus 23%) ($P = 0.030$). Finally, positive surgical margins were more common in patients with minor response than in patients with major response (18% versus 11%; $P = 0.033$). There was no association between the number of CLM and the response to preoperative chemotherapy ($P = 0.592$) or between necessity for major hepatectomy and the response to preoperative chemotherapy ($P = 0.944$).

When analyzing the association between morphologic response and pathologic response to preoperative chemotherapy, a close correlation between these factors was observed. In patients with type 1, type 2 and type 3 morphologic response, the percentage of patients with minor pathologic response was 7%, 13% and 81%, respectively. Surgical margin status was not, however, associated with the type of morphologic response to preoperative chemotherapy ($P = 0.333$).

Postoperative Mortality and Morbidity

The postoperative 90-day mortality rate was 3% (11 patients died). Three deaths were related to postoperative liver insufficiency in patients who underwent extended hepatectomy following prolonged preoperative chemotherapy (> 6 cycles). Four deaths were related to pulmonary or intra-abdominal infections, and 4 patients died of thromboembolic complications (myocardial infarction or pulmonary embolism). The postoperative 90-day morbidity rate was 28% (107/378 patients). Perioperative complications recorded using a standard grading system included 32 grade I, 12 grade II, 37 grade III, 15 grade IV and 11 grade V complications.[25] Sixteen percent of study patients experienced a major complication necessitating operative, endoscopic, or radiologic intervention.

Long-Term Survival

At a median follow-up time of 32 months (range, 1–118 months), the median survival for the entire cohort (n = 378) was 62 months. The 3-, 5-, and 10-year overall survival rates were 70%, 53%, and 21%, respectively. Patients who underwent R0 resection (n = 326) had a significantly better 5-year overall survival rate than those who underwent R1 resection (n = 52) (55% versus 26%, $P = 0.017$) (Figure 1).

The effect of surgical margin status on overall survival was analyzed in relation to morphologic tumor response to preoperative chemotherapy. Among the 65 patients with an optimal morphologic response, there was no difference in 3-year overall survival rates between patients with R0 and R1 resection (92% and 88%, respectively, $P = 0.917$) (Figure 2). In contrast, among the 137 patients with a suboptimal morphologic tumor response, the 5-year overall survival rate was significantly better following R0 resection (62% versus 11%, $P = 0.007$) (Figure 3).

Likewise, in patients with a major pathologic response to preoperative chemotherapy, 5-year overall survival rates were similar following R0 and R1 resection (63% and 67%, respectively, $P = 0.587$) (Figure 4). However, in patients with a minor pathologic response to preoperative chemotherapy, the 5-year overall survival rate was significantly better following R0 resection (46% versus 0%, $P = 0.002$) (Figure 5).

Predictors of Overall Survival

Results of analysis of predictors of overall survival in the entire cohort are shown in Table 2. On univariate analysis, predictors of worse overall survival were minor pathologic response ($P < 0.0001$), major postoperative complication ($P = 0.021$), need for blood transfusion ($P = 0.004$), multiple CLM ($P = 0.025$), diameter of the largest of the CLM ≥ 3 cm ($P = 0.002$),

and R1 resection ($P = 0.017$). On multivariate analysis, only minor pathologic response (hazard ratio [HR] 1.91, 95% CI 1.27–2.86, $P = 0.002$) and R1 resection (HR 1.69, 95% CI 1.05–2.74, $P = 0.03$) were independently associated with overall survival (Table 2).

In patients with major pathologic response to preoperative chemotherapy (Table 3), univariate analysis demonstrated that predictors of worse overall survival were primary rectal carcinoma ($P = 0.035$), regional lymph node metastases of the primary tumor ($P = 0.036$), and major postoperative complication ($P = 0.005$). On multivariate analysis, only major postoperative complication (HR 2.40, 95% CI 1.21–4.76, $P = 0.012$) remained as a significant predictor of survival (Table 3).

In patients with minor pathologic response to preoperative chemotherapy (Table 4), univariate analysis demonstrated that predictors of worse overall survival were multiple CLM ($P = 0.014$), diameter of the largest of the CLM ≥ 3 cm ($P = 0.039$), and R1 resection ($P = 0.002$). On multivariate analysis, R1 resection (HR 2.04, 95% CI 1.15–3.60, $P = 0.014$) was the only factor found to predict worse overall survival.

DISCUSSION

The gold standard for the surgical management of CLM is complete resection with histologically negative margins.[27] The current study confirms the importance of achieving an R0 resection in a homogeneous population treated with resection with curative intent after delivery of modern systemic chemotherapy consisting of oxaliplatin- or irinotecan-based regimens. Survival analysis of the entire patient cohort revealed a 5-year overall survival rate of 55% following R0 resection compared to 26% following R1 resection. These survival rates are similar to those reported in previous studies analyzing the impact of surgical margin status on outcome of patients with CLM.[15, 20, 28] These results are in contrast to a recently published study by de Haas et al. in which no difference in overall survival was identified between patients with R0 versus R1 resection.[19] Of note, however, only 73% of patients in that study were treated with preoperative systemic therapy and only 49% received contemporary chemotherapy regimens containing oxaliplatin or irinotecan. These differences in the delivery and composition of preoperative chemotherapy may explain the findings of each study.

In the current study, the magnitude of benefit associated with a negative margin was strongly influenced by the pathologic response to preoperative chemotherapy. For patients with a major pathologic response (0–49% residual viable tumor cells), surgical margin status did not impact survival: the 5-year overall survival rate was 63% following R0 resection and 67% following R1 resection. However, for patients with a minor pathologic response to preoperative chemotherapy (≥ 50% residual viable tumor cells), the 5-year overall survival rate was 46% following R0 resection and 0% following R1 resection although equivalent proportions of patients in the 2 groups received additional postoperative systemic therapy. In addition, multivariate analysis identified R1 margin as the only independent risk factor for poor survival in patients with a minor pathologic response to preoperative chemotherapy. These data indicate that postoperative systemic therapy cannot rescue patients from a combination of chemotherapy resistance and positive surgical margins and emphasize the dominant impact of tumor biology on outcomes.

Although pathologic response to preoperative chemotherapy was found to be a powerful predictor of long-term outcomes, it is obviously not available at the time of selection of patients for surgical resection of CLM. Given the frequent use of preoperative chemotherapy in patients with CLM,[29] a noninvasive method for evaluating tumor response to cytotoxic chemotherapy and predicting long-term outcomes would facilitate informed consent, risk

stratification, and the proper timing and sequence of tumor-directed therapy. In this regard, our group has published CT-based morphologic criteria that accurately predicted pathologic response to preoperative chemotherapy and correlated with overall survival in patients with CLM treated surgically and nonsurgically.[13] The analysis of CT morphologic criteria in this study is concordant with our previous results, further supporting its reliability as a predictor of pathologic response.

Although we would not suggest that clearly resectable patients be denied surgical therapy based on morphologic response to preoperative chemotherapy, the study supports the value of morphologic (CT-based) response in selecting patients with extensive disease for resection of CLM. For patients with an optimal morphologic response, no survival difference was observed between patients who underwent R0 and those who underwent R1 resection (3-year overall survival rates were 92% and 88%, respectively), indicating that operative therapy should proceed in this group even when close margins are anticipated by proximity of tumors to vascular structures. However, for patients with a suboptimal morphologic response, the 5-year overall survival rate was 62% following R0 resection compared to only 11% following R1 resection, suggesting that patients in this group who would be anticipated to have close margins may be better served with second line systemic therapies. Thus, the influence of surgical margin status in relation to CT-based morphologic response to chemotherapy mirrors the influence of surgical margin status in relation to pathologic response identified in surgical specimens. For a variety of malignancies, response to chemotherapy is known to be a sensitive marker for tumor biology and is recognized as an important prognostic indicator.[30–33] Previous data from our institution[12] and others[11] have demonstrated that degree of tumor cell killing in response to preoperative chemotherapy is a significant predictor of survival following hepatectomy for CLM. Similarly, in the current study, minor pathologic response was found to be an independent predictor of worse survival on multivariate analysis of the entire cohort. In light of these findings and the 0% 5-year survival rate in patients with a minor pathologic response to preoperative chemotherapy and R1 resection, aggressive surgical therapy should be pursued in patients with unfavorable tumor biology (as indicated by a suboptimal morphologic response to preoperative chemotherapy) only when a negative margin is clearly achievable. In contrast, in patients with an optimal morphologic response to preoperative chemotherapy, aggressive surgical therapy may be appropriate even if there is some concern that an R0 resection may not be achievable.

This study may be limited by its retrospective nature. It may also be limited by inclusion of patients treated with 2 different chemotherapy regimens, although the regimens were contemporary (oxaliplatin-based and irinotecan-based). Another potential limitation is that biologic agents that have been demonstrated to contribute to the effectiveness of cytotoxic therapy (i.e., bevacizumab)[6, 34] were not used in all cases. Despite these potential limitations, this represents the first study to examine the impact of surgical margin status in a homogeneous patient population treated with modern cytotoxic chemotherapy. Another possible limitation of this study is that morphologic response to preoperative therapy could not be evaluated in all patients as the criteria for morphologic response are currently CT-based and some patients had undergone magnetic resonance imaging or had tumors too small to permit an accurate qualitative assessment of response. This represents the second study to confirm the association between morphologic response to preoperative therapy, pathologic response to preoperative therapy, and long-term outcomes. In the future, we plan to further investigate these associations and to validate the morphologic response criteria using alternative imaging modalities, including magnetic resonance imaging.

In most studies on CLM, prognostic factors associated with survival after resection of CLM have included number, size, and distribution of hepatic lesions, the disease status of the

primary tumor lymph nodes, the disease-free interval before detection of CLM, and the preoperative CEA level.[28, 35] These prognostic factors are recorded either at initial presentation or prior to resection but are unrelated to preoperative treatment and variably reflect tumor biology. In this context, the predicted likelihood of achieving a microscopically negative surgical margin has always been a concern but has continued to be a point of controversy.[19] The current study, performed on a homogeneous cohort of patients who received preoperative chemotherapy with modern agents, serves to resolve some of this controversy. The findings indicate that patients with CLM and suboptimal response to preoperative chemotherapy are unlikely to benefit from surgery unless all tumors can be resected with microscopically negative margins.

In conclusion, this analysis supports a continued emphasis on achieving R0 resection in patients with CLM. The use of modern chemotherapy combined with aggressive surgical strategies has expanded the number of patients considered for resection of CLM and has resulted in improved long-term overall survival. For patients who demonstrate unfavorable tumor biology, as assessed by both traditional clinicopathologic criteria and more recently introduced imaging criteria, an aggressive surgical approach should be entertained only if an R0 resection is deemed feasible.

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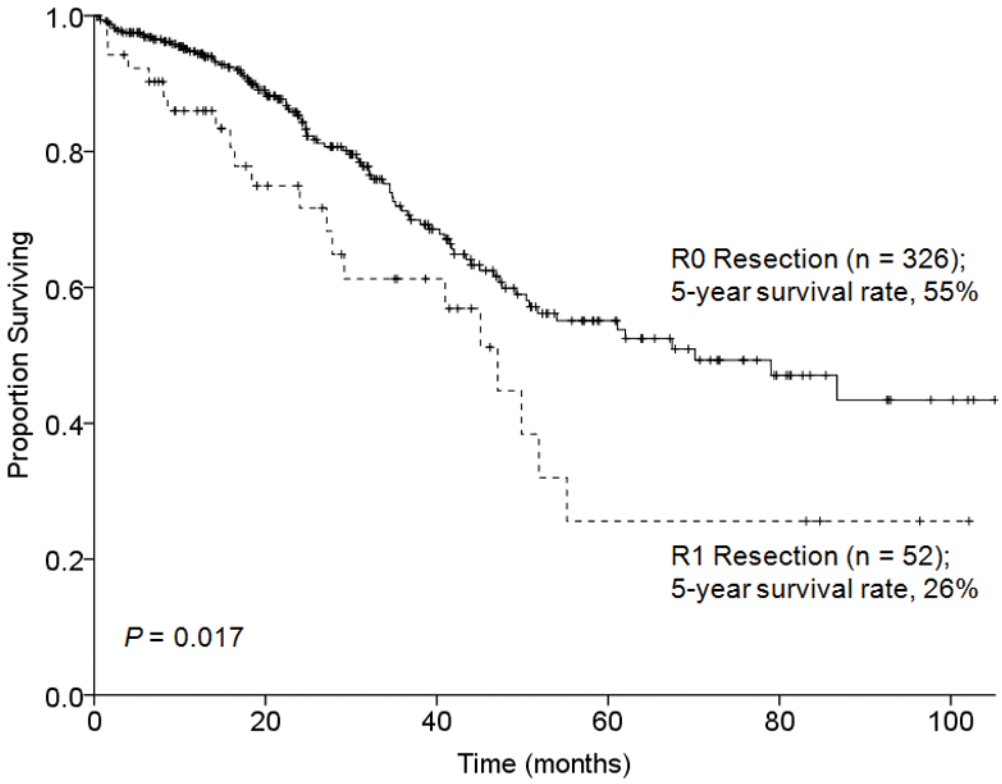

FIGURE 1.
Overall survival by surgical margin status in 378 patients who underwent hepatectomy for CLM after preoperative chemotherapy.

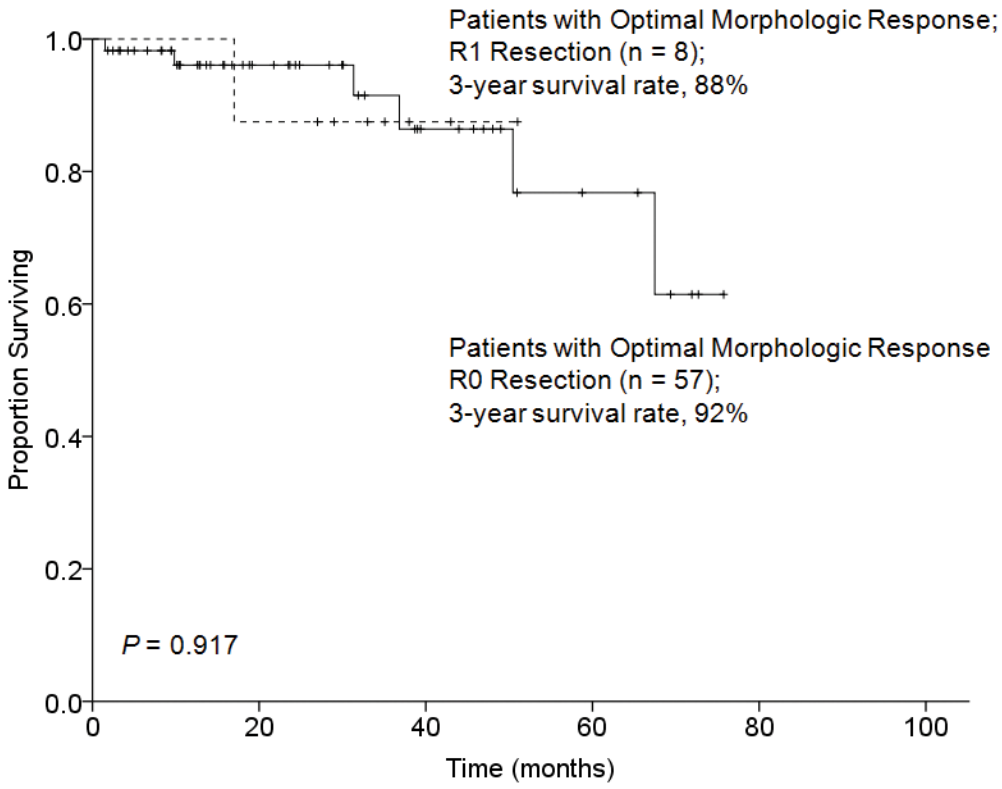

FIGURE 2.
Overall survival by surgical margin status in 65 patients who underwent hepatectomy for CLM and had an optimal morphologic response to preoperative chemotherapy.

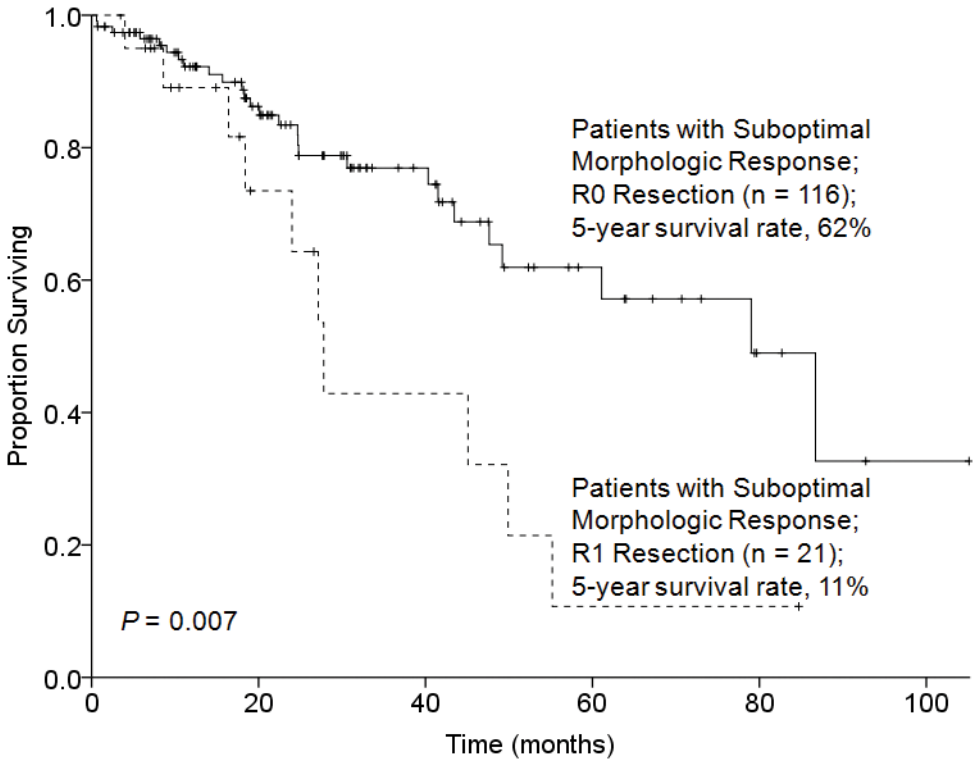

FIGURE 3.
Overall survival by surgical margin status in 137 patients who underwent hepatectomy for CLM and had a suboptimal morphologic response to preoperative chemotherapy.

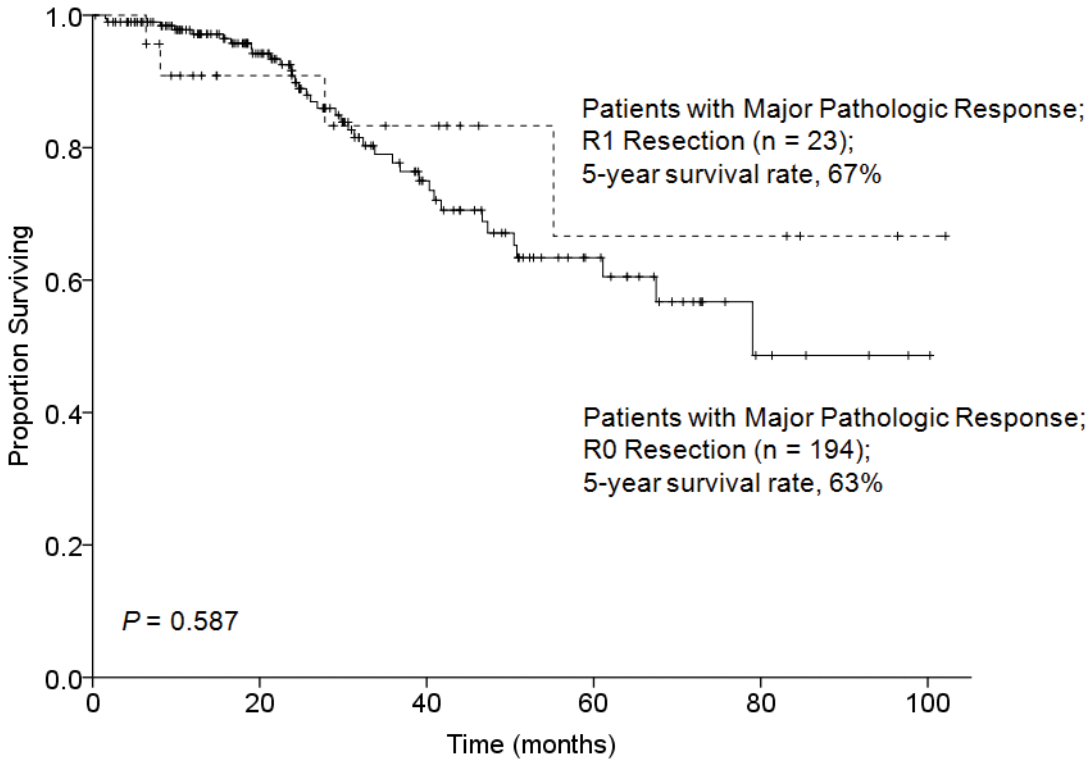

FIGURE 4.
Overall survival by surgical margin status in 217 patients who underwent hepatectomy for CLM and had a major pathologic response to preoperative chemotherapy.

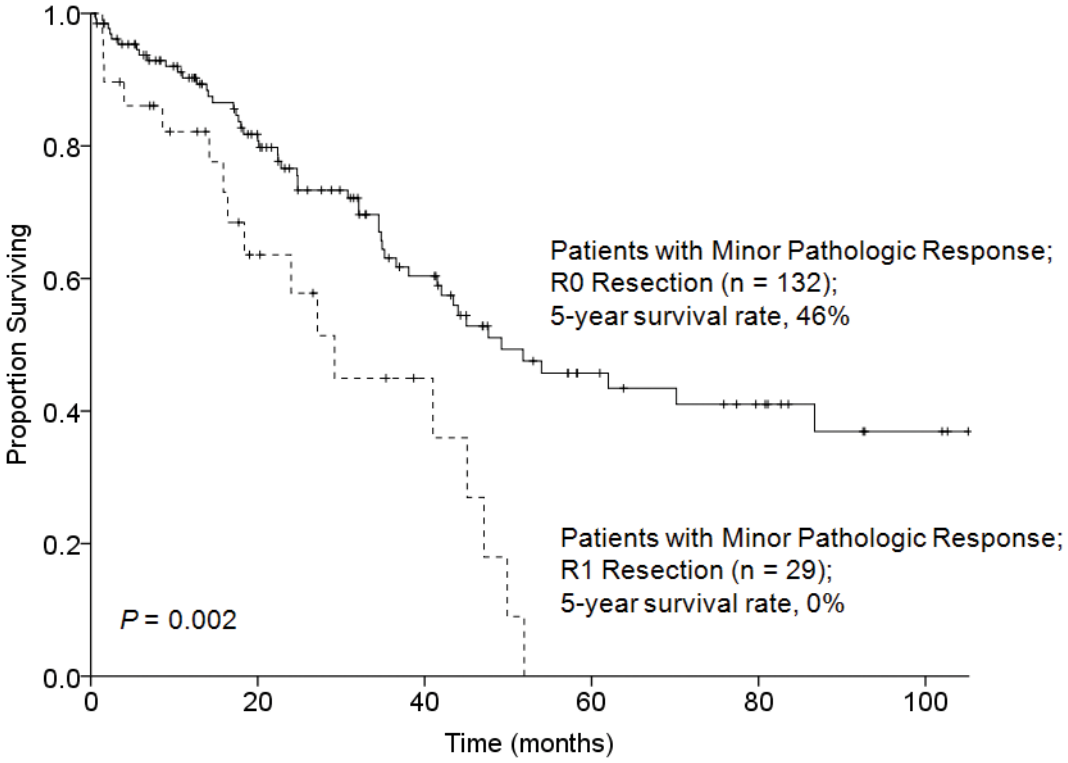

FIGURE 5.
Overall survival by surgical margin status in 161 patients who underwent hepatectomy for CLM and had a minor pathologic response to preoperative chemotherapy.

Table 1

Clinicopathologic Characteristics and Outcomes of 378 Patients who Underwent Hepatectomy for CLM According to the Pathologic Tumor Response to Preoperative Chemotherapy

Characteristic or Outcome	All Patients (N = 378)	Major Pathologic Response (N = 217)	Minor Pathologic Response (N = 161)	*P**
Male sex, n (%)	212 (56)	122 (56)	90 (56)	0.950
Median age (range), years	58 (25–85)	58 (25–85)	57 (27–82)	0.490
Mean age (SD), years	57 (11)	58 (11)	57 (12)	0.490
Median body mass index (range), kg/m^2	27 (16–48)	28 (18–48)	27 (16–48)	0.912
Mean body mass index (SD), kg/m^2	28 (6)	28 (6)	28 (6)	0.912
Synchronous CLM, n (%)	246 (65)	151 (70)	95 (59)	0.033
Rectal primary tumor, n (%)	105 (28)	52 (24)	53 (33)	0.055
Node-positive primary tumor, n (%)	267 (71)	156 (72)	111 (69)	0.534
Preoperative chemotherapy for CLM				
Irinotecan, n (%)	143 (38)	59 (27)	84 (52)	< 0.0001
Oxaliplatin, n (%)	235 (62)	158 (73)	77 (48)	< 0.0001
Bevacizumab, n (%)	230 (61)	147 (68)	83 (52)	0.001
Cetuximab, n (%)	21 (6)	13 (6)	8 (5)	0.668
Median number of cycles (range)	6 (2–36)	6 (2–32)	7 (2–36)	0.103
Mean number of cycles (SD)	8 (6)	8 (6)	9 (7)	0.103
Two-stage hepatectomy, n (%)	30 (8)	19 (9)	11 (7)	0.494
Portal vein embolization, n (%)	47 (12)	26 (12)	21 (13)	0.757
Associated procedure, n (%)	63 (17)	31 (14)	32 (20)	0.149
Major hepatectomy, n (%)	259 (69)	149 (69)	110 (68)	0.944
Postoperative complication, n (%)	107 (28)	54 (25)	53 (33)	0.086
Major postoperative complication, n (%)	61 (16)	32 (15)	29 (18)	0.390
Median estimated blood loss (range), mL	300 (0–6000)	300 (10–6000)	300 (0–3500)	0.070
Mean estimated blood loss (SD), mL	422 (512)	387 (502)	468 (523)	0.070
Blood transfusion, n (%)	68 (18)	31 (14)	37 (23)	0.030
Median number of CLM (range)	2 (1–75)	2 (1–75)	2 (1–16)	0.592
Mean number of CLM (SD)	3 (4)	3 (5)	3 (3)	0.592
Median largest diameter of CLM (range), cm	2 (1–18)	2 (1–16)	3 (1–18)	< 0.0001
Mean largest diameter of CLM (SD), cm	3 (3)	3 (2)	4 (3)	< 0.0001
Median preoperative CEA level (range), ng/mL	3 (0–1392)	2 (0–727)	5 (1–1392)	< 0.0001
Mean preoperative CEA level (SD), ng/mL	27 (106)	14 (63)	44 (143)	< 0.0001
Positive surgical margins, n (%)	52 (14)	23 (11)	29 (18)	0.033
Postoperative chemotherapy for CLM, n (%)	260 (69)	153 (71)	107 (67)	0.330

*Comparison of patients with major versus minor pathologic response.

CEA indicates carcinoembryonic antigen; CLM, colorectal liver metastases; SD, standard deviation.

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Table 2

Univariate and Multivariate Analysis of Clinicopathologic Variables Associated with Overall Survival in 378 Patients Who Underwent Hepatectomy for CLM after Preoperative Chemotherapy

				Multivariate Analysis*	
Variable	**N (%)**	**5-year Overall Survival Rate (%)**	**Univariate Analysis *P***	***P***	**Hazard Ratio (95% CI)**
Sex			0.085	NS	
Male	212 (56)	45			
Female	166 (44)	59			
Age			0.381		
≥ 60 years	164 (43)	48			
< 60 years	214 (57)	53			
Body mass index			0.417		
> 30 kg/m^2	126 (34)	48			
≤ 30 kg/m^2	250 (66)	54			
Timing of detection of CLM			0.205		
Synchronous	246 (65)	48			
Metachronous	132 (35)	57			
Primary tumor site			0.085	NS	
Rectum	105 (28)	39			
Colon	273 (72)	55			
Regional lymph nodes for primary tumor			0.340		
Positive	267 (71)	48			
Negative	111 (29)	57			
Preoperative chemotherapy			0.771		
Irinotecan	143 (38)	50			
Oxaliplatin	235 (62)	52			
Preoperative cetuximab			0.352		
Yes	21 (6)	0			
No	357 (94)	52			
Preoperative bevacizumab			0.873		
Yes	230 (61)	39			

Variable	N (%)	5-year Overall Survival Rate (%)	Univariate Analysis *P*	Multivariate Analysis* *P*	Multivariate Analysis* Hazard Ratio (95% CI)
No	148 (39)	53			
No. of cycles of chemotherapy			0.321		
≥ 6	151 (40)	48			
< 6	227 (60)	57			
Pathologic response to chemotherapy			< 0.0001	0.002	1.91 (1.27–2.86)
Major	217 (57)	64			
Minor	161 (43)	39			
Two-stage hepatectomy			0.685		
Yes	30 (8)	56			
No	348 (92)	51			
Portal vein embolization			0.193		
Yes	47 (12)	39			
No	331 (88)	53			
Associated procedure			0.320		
Yes	63 (17)	47			
No	315 (83)	52			
Major hepatectomy			0.337		
Yes	259 (69)	49			
No	119 (31)	58			
Major postoperative complication			0.021	NS	
Yes	61 (16)	40			
No	317 (84)	54			
Blood transfusion			0.004	NS	
Yes	68 (18)	37			
No	310 (82)	56			
Estimated blood loss			0.385		
> 1000 mL	24 (31)	45			
≤ 1000 mL	354 (69)	52			
Number of CLM			0.025	NS	
Multiple	233 (62)	45			

Variable	N (%)	5-year Overall Survival Rate (%)	Univariate Analysis *P*	Multivariate Analysis* *P*	Multivariate Analysis* Hazard Ratio (95% CI)
Single	145 (38)	61			
Maximum largest diameter of CLM			0.002	NS	
≥ 3 cm	186 (49)	44			
< 3 cm	192 (51)	61			
Preoperative CEA level			0.057	NS	
≥ 10 ng/mL	92 (24)	43			
< 10 ng/mL	286 (76)	54			
Margin status for resection of CLM			0.017	0.03	1.69 (1.05–2.74)
R1	52 (14)	26			
R0	326 (86)	55			
Postoperative chemotherapy for CLM			0.464		
Yes	260 (69)	49			
No	116 (31)	53			

*Cox regression multivariate analysis included all variables with $P < 0.1$ in univariate analysis.

CEA indicates carcinoembryonic antigen; CLM, colorectal liver metastases; NS, not significant; R0, surgical margin ≥ 1 mm; R1, no margin or surgical margin < 1 mm.

Table 3

Univariate and Multivariate Analysis of Clinicopathologic Variables Associated with Overall Survival in 217 Patients with Major Pathologic Tumor Response to Preoperative Chemotherapy for CLM

				Multivariate Analysis*	
Variable	**N (%)**	**5-year Overall Survival Rate (%)**	**Univariate Analysis *P***	***P***	**Hazard Ratio (95% CI)**
Sex			0.134		
Male	122 (56)	55			
Female	95 (44)	73			
Age					
≥ 60 years	95 (44)	54	0.255		
< 60 years	122 (56)	72			
Body mass index					
> 30 kg/m^2	73 (34)	58	0.842		
≤ 30 kg/m^2	144 (66)	66			
Timing of detection of CLM					
Synchronous	151 (70)	59	0.245		
Metachronous	66 (30)	72			
Primary tumor site			0.035	NS	
Rectum	52 (24)	43			
Colon	165 (76)	68			
Regional lymph nodes for primary tumor			0.036	NS	
Positive	156 (72)	57			
Negative	61 (28)	77			
Preoperative chemotherapy			0.174		
Irinotecan	59 (27)	68			
Oxaliplatin	158 (73)	61			
Preoperative cetuximab			0.240		
Yes	13 (6)	0			
No	204 (94)	66			
Preoperative bevacizumab			0.310		
Yes	147 (68)	57			

Variable	N (%)	5-year Overall Survival Rate (%)	Univariate Analysis *P*	Multivariate Analysis* *P*	Multivariate Analysis* Hazard Ratio (95% CI)
No	70 (32)	67			
No. of cycles of chemotherapy			0.116		
≥ 6	130 (60)	57			
< 6	87 (40)	75			
Two-stage hepatectomy			0.700		
Yes	19 (9)	64			
No	198 (91)	64			
Portal vein embolization			0.220		
Yes	26 (12)	43			
No	191 (88)	67			
Associated procedure			0.965		
Yes	31 (14)	78			
No	186 (86)	63			
Major hepatectomy			0.108		
Yes	149	59			
No	68	76			
Major postoperative complications			0.005	0.012	2.40 (1.21–4.76)
Yes	32 (15)	42			
No	185 (85)	68			
Blood transfusion			0.093	NS	
Yes	31 (14)	43			
No	186 (86)	68			
Estimated blood loss			0.850		
> 1000 mL	11 (5)	48			
≤ 1000 mL	206 (95)	65			
Number of CLM			0.850		
Multiple	127 (58)	60			
Single	90 (42)	69			
Maximum largest diameter of CLM			0.312		
≥ 3 cm	85 (39)	62			

Variable	N (%)	5-year Overall Survival Rate (%)	Univariate Analysis *P*	Multivariate Analysis* *P*	Multivariate Analysis* Hazard Ratio (95% CI)
< 3 cm	132 (61)	64			
Preoperative CEA level			0.939		
≥ 10 ng/mL	34 (16)	69			
< 10 ng/mL	183 (84)	63			
Margin status for resection of CLM			0.587		
R1	23 (11)	67			
R0	194 (89)	63			
Postoperative chemotherapy for CLM			0.261		
Yes	153 (71)	63			
No	62 (29)	62			

*Cox regression multivariate analysis included all variables with $P < 0.1$ in univariate analysis.

CEA indicates carcinoembryonic antigen; CLM, colorectal liver metastases; NS, not significant; R0, surgical margin ≥ 1 mm; R1, no margin or surgical margin < 1 mm.

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Table 4

Univariate and Multivariate Analysis of Clinicopathologic Variables Associated with Overall Survival in 161 Patients with Minor Pathologic Tumor response to Preoperative Chemotherapy for CLM

				Multivariate Analysis*	
Variable	**N (%)**	**5-year Overall Survival Rate (%)**	**Univariate Analysis *P***	***P***	**Hazard Ratio (95% CI)**
Sex			0.458		
Male	90 (56)	36			
Female	71 (44)	42			
Age			0.689		
≥ 60 years	69 (43)	40			
< 60 years	92 (67)	37			
Body mass index			0.355		
> 30 kg/m^2	53 (33)	37			
≤ 30 kg/m^2	106 (67)	40			
Timing of detection of CLM			0.202		
Synchronous	95 (59)	35			
Metachronous	66 (41)	44			
Primary tumor site			0.945		
Rectum	53 (33)	37			
Colon	108 (67)	39			
Regional lymph nodes for primary tumor			0.594		
Positive	111 (73)	39			
Negative	50 (29)	37			
Preoperative chemotherapy			0.705		
Irinotecan	84 (52)	38			
Oxaliplatin	77 (48)	37			
Preoperative cetuximab			0.656		
Yes	8 (5)	63			
No	153 (95)	38			
Preoperative bevacizumab			0.938		
Yes	83 (52)	15			

Variable	N (%)	5-year Overall Survival Rate (%)	Univariate Analysis *P*	Multivariate Analysis* *P*	Multivariate Analysis* Hazard Ratio (95% CI)
No	78 (48)	41			
No. of cycles of chemotherapy			0.994		
≥ 6	97 (60)	39			
< 6	64 (40)	38			
Two-stage hepatectomy			0.505		
Yes	11 (4)	44			
No	150 (96)	39			
Portal vein embolization			0.438		
Yes	21 (13)	34			
No	140 (87)	39			
Associated procedure			0.442		
Yes	32 (20)	31			
No	129 (80)	40			
Major hepatectomy			0.990		
Yes	110 (68)	39			
No	51 (32)	40			
Major postoperative complications			0.552		
Yes	29 (18)	38			
No	132 (82)	38			
Blood transfusion			0.096	NS	
Yes	37 (23)	33			
No	124 (77)	41			
Estimated blood loss			0.569		
> 1000 mL	13 (8)	39			
≤ 1000 mL	148 (92)	38			
Number of CLM			0.014	NS	
Multiple	55 (34)	32			
Single	106 (66)	52			
Maximum largest diameter of CLM			0.039	NS	
≥ 3 cm	101 (63)	32			

Variable	N (%)	5-year Overall Survival Rate (%)	Univariate Analysis *P*	Multivariate Analysis* *P*	Multivariate Analysis* Hazard Ratio (95% CI)
< 3 cm	60 (37)	55			
Preoperative CEA level			0.348		
≥ 10 ng/mL	103 (64)	33			
< 10 ng/mL	58 (36)	41			
Margin status for resection of CLM			0.002	0.014	2.04 (1.15–3.60)
R1	29 (18)	0			
R0	132 (82)	46			
Postoperative chemotherapy for CLM			0.859		
Yes	107 (66)	34			
No	54 (34)	45			

*Cox regression multivariate analysis included all variables with $P < 0.1$ in univariate analysis.

CEA indicates carcinoembryonic antigen; CLM, colorectal liver metastases; NS, not significant; R0, surgical margin ≥ 1 mm; R1, no margin or surgical margin < 1 mm.