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Resection after preoperative chemotherapy versus synchronous liver resection of colorectal cancer liver metastases

A propensity score matching analysis

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Abstract

This study aimed to determine the prognostic effects of preoperative chemotherapy for colorectal cancer liver metastasis (CLM).

We retrospectively evaluated 2 groups of patients between January 2006 and August 2012. A total of 53 patients who had ≥3 hepatic metastases underwent resection after preoperative chemotherapy (preoperative chemotherapy group), whereas 96 patients who had ≥3 hepatic metastases underwent resection with a curative intent before chemotherapy for CLM (primary resection group). A propensity score (PS) model was used to compare the both groups.

The 3-year disease-free survival (DFS) rates were 31.7% and 20.4% in the preoperative chemotherapy and primary resection groups, respectively (log-rank = 0.015). Analyzing 32 PS matched pairs, we found that the DFS rate was significantly higher in the preoperative chemotherapy group than in the primary resection group (3-year DFS rates were 34.2% and 16.8%, respectively [log-rank = 0.019]). Preoperative chemotherapy group patients had better DFSs than primary resection group patients in various multivariate analyses, including crude, multivariable, average treatment effect with inverse probability of treatment weighting model and PS matching.

Responses to chemotherapy are as important as achieving complete resection in cases of multiple hepatic metastases. Preoperative chemotherapy may therefore be preferentially considered for patients who experience difficulty undergoing complete resection for multiple hepatic metastases.

Abbreviations: CEA = carcinoembryonic antigen, CLM = colorectal cancer liver metastasis, CT = computed tomography, DFS = disease-free survival, IPW = inverse probability weighting, LVi = lympohovascular invasion, MRI = magnetic resonance imaging, OS = overall survival, PET = positron emission tomography, PH = proportional-hazards, PNi = perineural invasion, PS = Propensity scores, RFA = Radiofrequency ablation, SRS = stereotactic radiosurgery.

Keywords: colorectal cancer, liver metastases, preoperative chemotherapy

1. Introduction

An estimated 20% to 30% of colorectal cancer patients present with synchronous liver metastasis.[1] The 5- and 10-year survival rates after potentially curative resection range between 37% to 58% and 20% to 25%, respectively.[2] By contrast, the survival rates for untreated patients are very poor, as most of these patients succumb to the disease with a median survival of only 8 months.[2]

Surgical resection is the treatment of choice for patients with colorectal liver metastasis (CLM).[3,4] At the time of diagnosis, most patients with CLM present with advanced metastases, which are unresectable. Improvements in the outcomes of patients with CLM have been attributed to both advances in surgical techniques and the development of more effective chemotherapy.[5] Systemic chemotherapy has been increasingly used in preoperative settings for several reasons, that is, it may preoperatively reduce the tumor mass and increase the odds of achieving curative resection and/or the conversion of unresectable to resectable disease;[6–8] and chemotherapy can identify nonresponders who may not benefit from resection.[9] To characterize the prognostic effects of preoperative chemotherapy, we aimed in the present study to compare patients who

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underwent resection after preoperative chemotherapy for a CLM that was initially difficult to resect with patients who underwent synchronous hepatic resection for CLM. Furthermore, we used propensity score (PS)-based matching analysis to adjust for the diverse variables of the 2 groups.

2. Patients and methods

2.1. Patients

Between January 2006 and August 2012, 1245 patients with stage IV colorectal cancer underwent surgery at Asan Medical Center, Seoul, Korea. We divided these stage IV cancer patients into 2 groups—a primary resection and a preoperative chemotherapy group. Inclusion criteria for the primary resection group were as follows: histologically confirmed colorectal adenocarcinoma; stage IV cancer with metastasis to the liver alone; ≥3 hepatic metastases; and underwent surgery with a curative intent. Eligibility criteria for the preoperative chemotherapy group were as follows: histologically confirmed colorectal adenocarcinoma; stage IV cancer with metastasis to the liver alone; >3 hepatic metastases; chemotherapy followed by bowel and liver surgery; and underwent surgery with a curative intent. In general, rectal resection was simultaneously performed with minor hepatectomy (<3 segments) and major hepatectoy (≥3 segments) was simultaneously performed with (right-sided) colon resection.[10] Therefore, the patients with 1 or 2 hepatic metastasis mostly underwent simultaneous resection. To adjust the severity of metastasis to preoperative chemotherapy group, we enrolled the patients who had ≥3 hepatic metastases in both groups.

A total of 239 of 335 patients who underwent primary tumor hepatic metastasis resection before any chemotherapy were excluded because of 1 or 2 hepatic metastases. Ultimately, 96 patients were selected for inclusion in the primary resection group, which served as a control group. After excluding cases of R2 resection, extrahepatic metastasis, and no preoperative chemotherapy, a total of 53 patients were enrolled in the preoperative chemotherapy group.

A total of 149 patients were analyzed retrospectively. We defined synchronous liver metastases as cases with an intact primary tumor and metastasis only to the liver at the initial work-up.

The present study protocol was approved by the institutional review committee of Asan Medical Center.

2.2. Evaluation

Before treatment, all patients underwent a staging work-up that included the following steps: colonofiberscopy; chest radiography; computed tomography (CT) of the abdomen, pelvis, and chest; and a measurement of carcinoembryonic antigen (CEA) levels. A positron emission tomography (PET) scan was performed on patients who underwent surgery after 2007 because of national health insurance assistance. A single-contrast enhanced magnetic resonance imaging (MRI) assessment of the liver was performed to further characterize the malignancy risk of each lesion in cases of equivocal findings in the CT scan. Generally, tumors were pathologically staged, but those patients who underwent bowel surgery after chemotherapy in the preoperative chemotherapy group or bowel surgery after preoperative chemoradiotherapy in the primary resection group were clinically staged.

Table 1

Preoperative and adjuvant chemotherapy regimens.

	Preoperative chemotherapy group (n = 53)	Primary resection group (n = 96)
	1st line chemotherapy (n = 44)	Adjuvant chemotherapy
Irinotecan-based	20	14
FOLFIRI	15	10
XELIRI	3	2
Irinotecan + Ts-1	2	0
FOLFIRIAV	0	2
Oxaliplatin-based	23	64
FOLFOX	8	20
XELOX	7	42
FOLFOXAV	3	0
XELOXAV	4	1
FOLFOXER	1	1
Xeloda	1	7
Intra-arterial chemotherapy	0	3
Other hospital	0	4
No chemotherapy	0	4
Multiple lines of chemotherapy	9	0

AV = avastin (bevacizumab), ER = Erbitux (cetuximab), FOLFIRI = 5-FU + leucovoric + irinotecan, FOLFOX = 5-FU + leucovorin + oxaliplatin, XELIRI = Xeloda (capecitabine) + irinotecan, XELOX = xeloda + oxaliplatin.

2.3. Chemotherapy

For patients in the preoperative chemotherapy group who received first-line chemotherapy, tumor responses were assessed every 3 to 4 cycles using the Response Evaluation Criteria in Solid Tumors (RECIST).[11,12] For cases of progressive disease, treatment was switched to other chemotherapy regimens. A total of 9 (16.9%) of 53 patients received multiple types of preoperative chemotherapy. In the primary resection group, 92 (95.8%) of 96 patients received chemotherapy for adjuvant treatment (Table 1).

2.4. Treatment

In the preoperative chemotherapy group, 18 (33.9%) of 53 patients underwent a 2-stage operation (Fig. 1). The patients who were expected to have bowel complication (obstruction or perforation) underwent bowel surgery first before chemotherapy. Different surgical techniques were used to enable resection. Portal vein embolization was performed on 1 patient in the preoperative chemotherapy group. The 3 patients who were expected to have small remnant liver volume after hepatectomy had 2-stage heptatectomy. Radiofrequency ablation (RFA) or stereotactic radiosurgery (SRS) was used with hepatectomy. They were used exclusively for multiple bilateral metastases in cases of liver resection that were otherwise difficult to resect more normal liver parenchyma because of the extent of liver resection. The decisions to perform surgery before or after chemotherapy were made during a multidisciplinary team meeting including surgeons, medical oncologist, and radiologist. The general concept whether preoperative chemotherapy would be used or not was depending on remnant liver volume at least 30% of nontumoral liver parenchyma after performing curative surgery.

2.5. Follow-up

Patients underwent physical examinations, abdomen and pelvic CT scans, chest radiography, and measurements of serum CEA levels every 3 months during the first 2 years, and thereafter

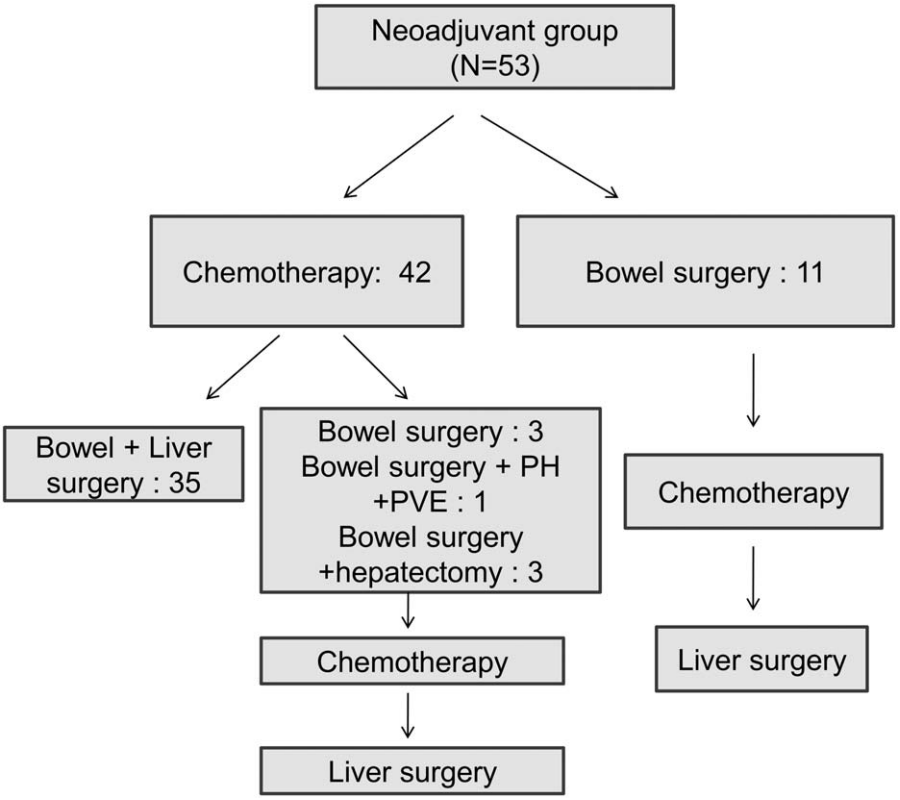

Figure 1. Sequence of treatments in the preoperative chemotherapy group.

at 6-month intervals. CT scans of the chest, MRI assessments of the liver, and PET scans were performed when recurrence was suspected.

2.6. Statistical analysis

Categorical variables were compared using Fisher exact test or Pearson χ^2 test, as appropriate, and continuous variables were compared using the Mann-Whitney *U* test or Student *t* test. To reduce the effect of selection bias in the assignment of patients to preoperative chemotherapy, we performed a rigorous adjustment of differences in baseline characteristics by propensity score-based methods. After propensity-score estimation, primary resection group and preoperative chemotherapy group were matched according to propensity score in a 1:1 ratio without replacement (greedy-matching algorithm), with a caliper equal to 0.15 of the standard deviation of the logit of the propensity score. Standardized differences were estimated for all the baseline covariates before and after matching to assess prematch imbalance and postmatch balance. The comparative risks of recurrence-free survivals were further adjusted for in the matched cohort with the use of a Cox proportional-hazards (PH) regression model that was stratified on the matched pair to account for the correlated properties of matching. Also, inverse probability weighting (IPW) that was based on the propensity score was then used as the primary tool to adjust for differences between the 2 treatment groups. We verified the performance of the propensity model by performing weighted 2-sample *t* test and weighted χ^2 test for the distribution of covariates and propensity scores between 2 treatment groups after inverse probability weighting. We carried out a cox PH regression on recurrence-free survival with IPW using the propensity score.

The final model for the multivariable cox PH model included age, sex, number of liver metastasis, largest size of liver metastasis, lympohovascular invasion (LVi), perineural invasion (PNi), T category, N category, and use of RFA and/or SRS. The survival curves were estimated with the use of the Kaplan-Meier method and presented in PS-based matched data. All tests of significance were 2-tailed and $P < 0.05$ was considered significant. All statistical analyses were performed in R 2.14.2 (http://www.r-project.org).

3. Results

3.1. Patient characteristics

The characteristics of the patients in the 2 groups are summarized in Table 2. The median follow-up periods were 39.7 months (range, 9.8–88.0 months) and 33.9 months (1.0–109.4 months) in the preoperative chemotherapy and primary resection groups, respectively. The mean number of liver metastases in the preoperative chemotherapy and primary resection groups were 6.4 ± 3.2 and 4.0 ± 1.6, respectively ($P = 0.002$). The mean diameters of the largest liver metastasis in the preoperative chemotherapy and primary resection groups were 4.8 ± 3.1 and 3.0 ± 2.1 cm, respectively ($P < 0.001$). A total of 15 (28.3%) of 53 patients were treated with liver resection and RFA and/or SRS in the preoperative chemotherapy group, whereas 26 (27.1%) of 98 patients were treated by this approach in the primary resection group ($P = 0.873$).

3.2. Operative data

In the preoperative chemotherapy group, 18 (33.9%) of 53 patients underwent a 2-stage operation. Among these patients, 11 patients underwent bowel surgery before chemotherapy, and the

Table 2

The clinicopathologic characteristics of patients in the preoperative and primary resection groups.

	Preoperative chemotherapy group (n = 53)	Primary resection group (n = 96)	*P*
Age, y			0.727
Mean ± SD	59 ± 10	59 ± 9	
Sex			0.038
Male	35 (66.0)	78 (81.3)	
Female	18 (34.0)	18 (18.8)	
CEA, ng/mL	189.6 ± 602.7	80.3 ± 468.3	0.221
Primary tumor			0.339
Rectum	19 (36.5)	42 (44.7)	
Histology			0.525
WD, MD	46 (88.5)	88 (91.7)	
PD, Muc	6 (11.5)	8 (8.3)	
T stage*			0.280
T2	3 (5.7)	2 (2.1)	
T3	47 (88.7)	83 (86.5)	
T4	3 (5.7)	11 (11.5)	
N stage*			0.371
N0	5 (9.4)	17 (17.7)	
N1	24 (45.3)	37 (38.5)	
N2	24 (45.3)	42 (43.8)	
LVi	20 (37.7)	42 (43.8)	0.476
PNi	9 (17.0)	35 (36.5)	0.013
Liver metastasis			
No. of metastases			<0.001
Mean ± SD	6.4 ± 3.2	4.0 ± 1.6	
Size of metastases, cm			<0.001
Mean ± SD	4.8 ± 3.1	3.0 ± 2.1	
Treatment			0.873
Resection only	38 (71.7)	70 (72.9)	
Combined treatment†	15 (28.3)	26 (27.1)	
Follow-up mo			
Median, mo (range)	39.7 (9.8–88.0)	33.9 (1.0–109.4)	

LVi = lymphovascular invasion, MD = moderately differentiated, MUC = mucinous, PD = poorly differentiated, PNi = perineural invasion, SD = standard deviation, WD = well differentiated.

* Most patients were staged pathologically; 42 patients of 53 in preoperative chemotherapy group who underwent chemotherapy before surgery and 13 patients of 96 in primary resection group who underwent preoperative chemoradiotherapy were staged clinically.

† Resection and radiofrequency ablation and/or stereotactic radiosurgery.

liver resection surgery was completed soon thereafter. For 3 patients who underwent bowel surgery after preoperative chemotherapy, additional chemotherapy and liver surgery were completed afterwards. Another 1 patient underwent bowel surgery and incomplete liver surgery with portal vein embolization, and similarly additional chemotherapy and liver surgery were completed thereafter. The remaining 3 patients underwent bowel surgery and incomplete liver resection after preoperative chemotherapy, and additional chemotherapy and liver surgery were completed thereafter (Fig. 1). There were no instances of in-hospital mortality after surgery.

3.3. Survival and risk factors in all patients and matched patients

The disease-free survival (DFS) rate was significantly higher in the preoperative chemotherapy group than in the primary resection group (3-year DFS rates were 31.7% and 20.4%, respectively (log-rank = 0.015; Fig. 2A)). There was no difference in overall survival (OS) rate (3-year OS rates were 77.2% and 64.6% in the preoperative chemotherapy and primary resection groups, respectively (log-rank = 0.287)).

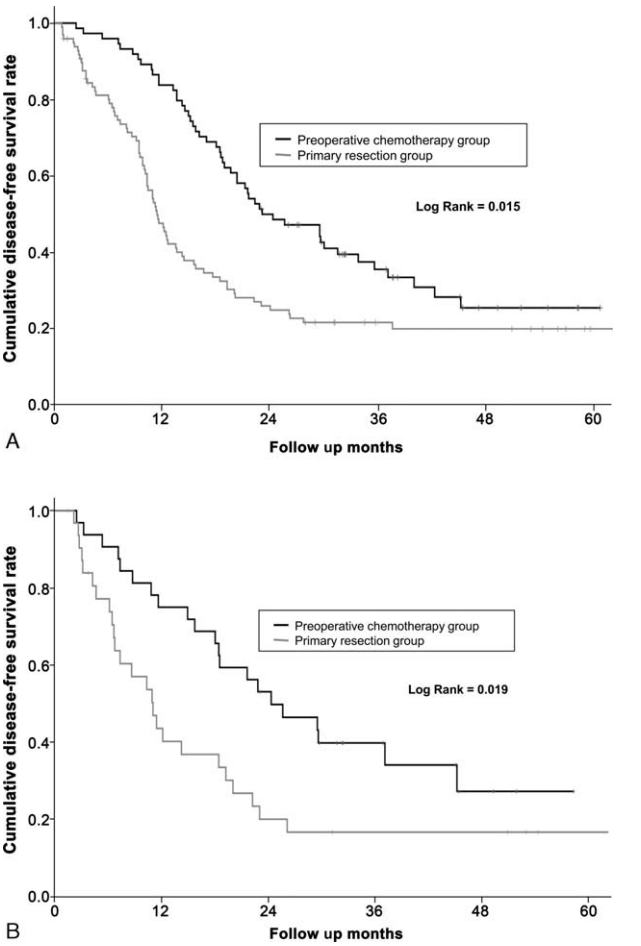

Figure 2. Disease-free survival curves of the preoperative chemotherapy and primary resection groups: (A) in all patients (N = 149) and (B) in PS-based matched patients (N = 64).

To reduce the effect of selection bias, we performed an adjustment of differences in baseline characteristics by PS based methods. Propensity scores (PS) were estimated without regard to outcomes, using multiple logistic regression analysis with all prespecified covariables listed in Table 3 (age, sex, number of liver metastasis, largest size of liver metastasis, LVi, PNi, T category, N category, use of RFA and/or SRS). Model discrimination was assessed with c-statistics (c = 0.848), and model calibration with Hosmer-Lemeshow statistics ($P = 1.000$).

We consequently analyzed the matched 32 pairs of cases. The DFS rate was significantly higher in the preoperative chemotherapy group than in the primary resection group (3-year DFS rates were 34.2% and 16.8%, respectively (log-rank = 0.019; Fig. 2B)). There was no difference in OS rate (3-year OS rates were 74.7% and 62.2% in the preoperative chemotherapy and primary resection groups, respectively (log-rank = 0.244)).

Preoperative chemotherapy group patients had better DFSs than primary resection group patients in various multivariate analyses, including average treatment effect (ATE) with IPTW model and PS matching (Table 4).

4. Discussion

Liver metastases from colorectal cancers represent the leading cause of cancer-related morbidity and mortality. Most patients

Table 3

Comparison of clinicopathologic characteristics after propensity score matching.

	Preoperative chemotherapy group (n = 32)	Primary resection group (n = 32)	SMD
Age, y			−0.095
Mean ± SD	59 ± 10	59 ± 8	
Sex			0.068
Male	23 (71.9)	22 (68.7)	
Female	9 (28.1)	10 (31.3)	
s-CEA			0.065
Normal	12 (37.5)	11 (34.4)	
High	20 (62.5)	21 (65.6)	
Primary tumor			0.065
Colon	20 (62.5)	21 (65.6)	
Rectum	12 (37.5)	11 (34.4)	
T stage*			−0.031
T1/2	1 (3.1)	2 (6.2)	
T3/4	31 (96.9)	30 (93.8)	
N stage*			0.068
Node negative	5 (15.6)	5 (15.6)	
Node positive	27 (84.4)	27 (84.4)	
LVi	20 (62.5)	19 (59.4)	0.064
PNi	23 (71.9)	23 (71.9)	0
Liver metastasis			
No. of metastases			0.158
Mean ± SD	5.4 ± 2.2	5.1 ± 2.2	
Size of metastases, cm			−0.031
Mean ± SD	3.9 ± 2.8	4.0 ± 2.6	
Treatment			0.129
Resection only	11 (34.4)	13 (40.6)	
Combined treatment†	21 (65.6)	19 (59.4)	

LVi = lymphovascular invasion, PNi = perineural invasion, SD = standard deviation, SMD = standardized mean difference.

* Most patients were staged pathologically; 25 patients of 32 in preoperative chemotherapy group who underwent chemotherapy before surgery and 2 patients of 32 in primary resection group who underwent preoperative chemoradiotherapy were staged clinically.

† Resection and radiofrequency ablation and/or stereotactic radiosurgery.

Table 4

Preoperative chemotherapy effect using various statistical methods.

Method	N	HR (95% CI)	P
Crude	149	0.606 (0.410–0.897)	0.012
Multivariable	149	0.504 (0.302–0.847)	0.009
ATE using IPTW model	149	0.508 (0.339–0.760)	<0.001
PS matching	64	0.491 (0.282–0.854)	0.012

ATE = Average treatment effect, CI = confidence interval, HR = hazard ratio, IPTW = inverse probability of treatment weighting, PS = propensity score.

with colorectal liver metastases present with unresectable disease, whereas surgical resection is certainly the best treatment for resectable liver metastases. The survival benefits of patients associated with a radical surgical approach resulted from the selection of patients based on preoperative chemotherapy who exhibited unfavorable tumor characteristics, but who were responsive to chemotherapy and could undergo complete resection for metastatic disease.[5,13] The traditional limits for hepatic resection can now be exceeded as advancements in hepatic surgery and postoperative patient management allows for the safe resection of up to two-thirds of the functional liver parenchyma, which is associated with a mortality of ≤5% at major centers.[14–16]

Previous studies have reported that modern chemotherapy allows 12.5% of patients with unresectable CLM to be rescued by liver surgery with a long-term survival similar to that reported for a priori surgical candidates.[7,17] The importance of preoperative chemotherapy was highlighted by the same research group who suggested that tumor progression before surgery was associated with a poor outcome, even though potentially curative surgery and tumor control before surgery were crucial for achieving prolonged remission in patients with CLM.[9] Currently, an ongoing study is using preoperative chemotherapy, including a targeted regimen.[18] In our present study, we used various chemotherapy regimens to induce a response. Most patients responded to first-line chemotherapy; however, 9 (16.9%) of 53 patients did not respond to first-line chemotherapy and were instead treated by multiple lines of chemotherapy.

Inclusion in our preoperative chemotherapy group was a significant positive prognostic factor for DFS compared with inclusion in the primary resection group for patients who had ≥3 hepatic metastases. It is possible that the preoperative chemotherapy group included better responders to chemotherapy, although the primary resection group included both responders and nonresponders to chemotherapy. Some studies have reported a relationship between responses to preoperative chemotherapy and survival. Blazer et al[19] suggested that a pathological response to preoperative chemotherapy was a predictor of survival. Furthermore, another study asserted that liver resection could improve long-term survival in patients with multiple CLM if the metastatic disease had been controlled by chemotherapy before surgery.[9] From this perspective, the importance of preoperative chemotherapy was to identify patients who would respond to chemotherapy.

The effectiveness of liver resection for bilobar and multiple metastases remains controversial. Some studies have reported no significant difference in the survival rate after liver resection between patients with solitary liver metastasis and those with multiple liver metastases.[15,20,21] Nevertheless, the general consensus is that patients with ≥3 hepatic metastases gain little benefit from liver resection.[22–24] The recent studies reported that >3 hepatic metastases were associated with increased risk of recurrence.[25,26] At our center, the number of metastases has never been considered to be a contraindication to the offer of surgery if a complete resection was technically possible. We adopted this policy because complete resection of hepatic metastases is the only way to provide these patients with a chance of achieving long-term remission, in contrast to the use of chemotherapy alone.[9]

In this present study, when the patients were not candidates for complete resection, they were instead considered for combined resection plus RFA and/or SRS. Dominant lesions were resected, whereas other lesions located in deep sites of the liver were ablated. One previous study compared hepatic resection, RFA, and combined resection plus RFA and found that OS was highest in the resection group and recurrence was lowest in the resection group compared with the RFA plus resection and RFA-alone groups.[3] Some studies have reported that the local recurrence rates with RFA are not significantly different from patients who had undergone anatomic or wedge resections of the liver.[27] Another study reported that DFS and OS did not differ between the RFA and resection groups with a solitary CLM <3 cm.[28,29] A further study of patients who underwent preoperative chemotherapy reported that there was no difference in DFS versus OS between the resection and resection plus cryotherapy groups after preoperative chemotherapy.[30] Therefore, we included this variable for adjustment of baseline characteristics.

In this study, to reduce the effect of selection bias, we performed a rigorous adjustment of these baseline characteristics (age, sex, number of liver metastasis, largest size of liver metastasis, lymphovascular invasion, perineural invasion, T category, N category, and use of RFA and/or SRS). After the PS-based matched data, the DFS rate was significantly higher in the preoperative chemotherapy group than in the primary resection group.

This study was limited by its retrospective design, which introduced an inevitable selection bias for the 2 groups. The preoperative chemotherapy group had by definition an advanced disease because of the difficulty of the surgery. By contrast, the primary resection group had by definition a less advanced disease because of the relative ease of surgery. It may not be possible to enroll these 2 groups as a comparative group because the proper treatment for each group of patients is different. PS-based matched date can only adjust for observed confounders and not for unobserved confounders. Many factors may influence recurrence after surgery and it is difficult to deal with them all at the same time. Thus, this PS-based matched data analysis and IPTW models will not eliminate all selection bias. However, these methods can minimize selection bias.

In conclusion, to find out the responders of the chemothreapy is as important as achieving complete resection in cases of multiple hepatic metastases. Therefore, we might preferentially consider preoperative chemotherapy for patients who experience difficulty undergoing complete resection for multiple hepatic metastases (i.e., $\geq$3).

References

[1] Jaeck D, Bachellier P, Guiguet M, et al. Long-term survival following resection of colorectal hepatic metastases. Association Française de Chirurgie. Br J Surg 1997;84:977–80.

[2] Simmonds PC, Primrose JN, Colquitt JL, et al. Surgical resection of hepatic metastases from colorectal cancer: a systematic review of published studies. Br J Cancer 2006;94:982–99.

[3] 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;239:818–25. discussion 825-817.

[4] Minagawa M, Makuuchi M, Torzilli G, et al. Extension of the frontiers of surgical indications in the treatment of liver metastases from colorectal cancer: long-term results. Ann Surg 2000;231:487–99.

[5] Kopetz S, Chang GJ, Overman MJ, et al. Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy. J Clin Oncol 2009;27:3677–83.

[6] Parikh AA, Gentner B, Wu TT, et al. Perioperative complications in patients undergoing major liver resection with or without neoadjuvant chemotherapy. J Gastrointest Surg 2003;7:1082–8.

[7] Adam R, Delvart V, Pascal G, et al. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. Ann Surg 2004;240:644–57. discussion 657-648.

[8] Imai K, Allard MA, Castro Benitez C, et al. Nomogram for prediction of prognosis in patients with initially unresectable colorectal liver metastases. Br J Surg 2016;103:590–9.

[9] Adam R, Pascal G, Castaing D, et al. Tumor progression while on chemotherapy: a contraindication to liver resection for multiple colorectal metastases? Ann Surg 2004;240:1052–61. discussion 1061-1054.

[10] Ihnat P, Vavra P, Zonca P. Treatment strategies for colorectal carcinoma with synchronous liver metastases: Which way to go? World J Gastroenterol 2015;21:7014–21.

[11] Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000;92:205–16.

[12] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer (Oxford, England: 1990) 2009;45:228–47.

[13] 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;29:1083–90.

[14] Doci R, Gennari L, Bignami P, et al. Morbidity and mortality after hepatic resection of metastases from colorectal cancer. Br J Surg 1995;82:377–81.

[15] Scheele J, Stang R, Altendorf-Hofmann A, et al. Resection of colorectal liver metastases. World J Surg 1995;19:59–71.

[16] Welsh FK, Tilney HS, Tekkis PP, et al. Safe liver resection following chemotherapy for colorectal metastases is a matter of timing. Br J Cancer 2007;96:1037–42.

[17] Adam R, Avisar E, Ariche A, et al. Five-year survival following hepatic resection after neoadjuvant therapy for nonresectable colorectal. Ann Surg Oncol 2001;8:347–53.

[18] Folprecht G, Gruenberger T, Bechstein WO, et al. Tumour response and secondary resectability of colorectal liver metastases following neo-adjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial. Lancet Oncol 2010;11:38–47.

[19] Blazer DG, Kishi Y, Maru DM, et al. Pathologic response to preoperative chemotherapy: a new outcome end point after resection of hepatic colorectal metastases. J Clin Oncol 2008;26:5344–51.

[20] Fortner JG, Silva JS, Golbey RB, et al. Multivariate analysis of a personal series of 247 consecutive patients with liver metastases from colorectal cancer. I. Treatment by hepatic resection. Ann Surg 1984;199:306–16.

[21] Adson MA, van Heerden JA, Adson MH, et al. Resection of hepatic metastases from colorectal cancer. Arch Surg 1984;119:647–51.

[22] Iwatsuki S, Dvorchik I, Madariaga JR, et al. Hepatic resection for metastatic colorectal adenocarcinoma: a proposal of a prognostic scoring system. J Am Coll Surg 1999;189:291–9.

[23] Resection of the liver for colorectal carcinoma metastases: a multi-institutional study of indications for resection. Registry of Hepatic Metastases. Surgery 1988;103:278–88.

[24] August DA, Sugarbaker PH, Ottow RT, et al. Hepatic resection of colorectal metastases. Influence of clinical factors and adjuvant intraperitoneal 5-fluorouracil via Tenckhoff catheter on survival. Ann Surg 1985;201:210–8.

[25] Hallet J, Sa Cunha A, Adam R, et al. Factors influencing recurrence following initial hepatectomy for colorectal liver metastases. Br J Surg 2016;103:1366–76.

[26] Jang KU, Kim CW, Kim KH, et al. Prognostic factors in terms of the number of metastatic nodules in patients with colorectal cancer liver metastases. Ann Coloproctol 2016;32:92–100.

[27] Elias D, Baton O, Sideris L, et al. Local recurrences after intraoperative radiofrequency ablation of liver metastases: a comparative study with anatomic and wedge resections. Ann Surg Oncol 2004;11:500–5.

[28] Kim KH, Yoon YS, Yu CS, et al. Comparative analysis of radiofrequency ablation and surgical resection for colorectal liver metastases. J Korean Surg Soc 2011;81:25–34.

[29] Lee BC, Lee HG, Park IJ, et al. The role of radiofrequency ablation for treatment of metachronous isolated hepatic metastasis from colorectal cancer. Medicine 2016;95:e4999.

[30] Rivoire M, De Cian F, Meeus P, et al. Combination of neoadjuvant chemotherapy with cryotherapy and surgical resection for the treatment of unresectable liver metastases from colorectal carcinoma. Cancer 2002;95:2283–92.