Journal of Surgical Oncology 2014;109:239–244

Palliative Surgery in Patients With Unresectable Colorectal Liver Metastases: A Propensity Score Matching Analysis

YONG SIK YOON, MD,[1] CHAN WOOK KIM, MD,[1] SEOK-BYUNG LIM, MD,[1] CHANG SIK YU, MD,[1] SO YEON KIM, MD,[2] TAE WON KIM, MD,[3] MIN-JU KIM, BS,[4] AND JIN CHEON KIM, MD[1]*

[1]Department of Surgery, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea
[2]Department of Radiology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea
[3]Department of Internal Medicine, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea
[4]Departments of Clinical Epidemiology and Biostatistics, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea

Background and Objectives: The current study was primarily intended to determine the best surgical treatment for patients with unresectable liver metastatic colorectal cancer (CRC). In addition, we assessed whether the improvement in survival resulting from palliative resection (PR) of the primary tumor was a function of the extent of liver metastasis.

Methods: The demographics, tumor characteristics, and survival outcomes of 261 patients who underwent palliative surgery for unresectable liver metastatic CRC were analyzed. A propensity-score model was used to compare the group of patients receiving PR and non-resection (NR).

Results: There were 195 PR patients and 66 NR. The median survival of PR and NR patients was 21 months and 10 months, respectively ($P < 0.001$). In a Cox multivariate analysis of 51 propensity-score matched pairs, PR resulted in longer survival than NR (Hazard Ratio for NR 1.481; 95% confidence interval: 1.003–2.185; $P = 0.048$). The extent of liver metastasis only led to better survival of PR than NR patients among patients with limited liver metastasis not among those with extensive liver metastasis ($P = 0.001$).

Conclusions: PR appears to result in better survival than NR when the patient's overall condition permits an aggressive approach, especially in patients with limited liver metastases.

J. Surg. Oncol. 2014;109:239–244. © 2013 Wiley Periodicals, Inc.

KEY WORDS: **Colorectal adenocarcinomas; surgical treatment; survival; propensity score matching**

INTRODUCTION

Twenty percent of colorectal cancer (CRC) patients will have stage IV disease at diagnosis, and of these patients, 75–90% will have unresectable metastases and therefore require palliative management [1]. Various treatment options are available for patients with stage IV CRC. Depending on the extent of metastasis, performance status, and the presence of obstructions, the first-line treatment can be chemotherapy or surgery [2]. First-line chemotherapy regimens for asymptomatic patients with unresectable metastatic CRC include fluorouracil with leucovorin and irinotecan or oxaliplatin (alone or combined with targeted agents). These regimens have improved the median survival of patients with unresectable metastatic CRC from 6 months to 2 years [3–5]. Neoadjuvant chemotherapy is a treatment option in CRC patients with resectable liver metastases [6,7].

Many studies of unresectable metastatic CRC have focused on "palliative resection (PR) vs. chemotherapy" as first-line treatment, but investigations evaluating "PR vs. non-resection (NR)" are relatively rare [8,9]. In symptomatic patients with unresectable metastatic CRC, palliative surgery including PR and NR of primary tumor (stoma construction or bypass surgery) should be considered as the first-line treatment. Some studies have shown a survival benefit of resection of the primary tumor vs. its NR [8–10]. However, there have been few studies of effect of resection of the primary tumor on the survival of patients with extensive metastatic CRC [8].

The present study was primarily intended to determine the best surgical treatment for patients with unresectable colorectal liver metastases. In addition, we aimed to assess whether the survival benefit of PR of the primary tumor depends on the extent of liver metastasis.

MATERIALS AND METHODS

Patients and Parameters

Prospective CRC data collected at our tertiary referral center over an 8-year period (2000–2007) were reviewed. Among 6,379 consecutive primary CRC patients who underwent surgery, we identified 1,040 patients (16.3%) who had with stage IV CRC. Of these patients, 518 patients had liver-only metastases, and 257 patients who received curative intent surgery (R0 or R1) were excluded. Finally, 261 patients who underwent palliative surgery (R2) as first-line treatment were analyzed. These patients had liver metastases judged unresectable because of invasion of major liver pedicles (metastatic disease adjacent to or involving all three hepatic veins, and/or the portal vein bifurcation, and/or the retrohepatic vena cava, and/or the vascular structures of the

Grant sponsor: Asan Institute for Life Sciences;
Grant number: 2013-069.Grant number: 9-490.; Grant sponsor: Korea Health 21 R&D Project;
Grant number: A062254.; Grant sponsor: Center for Development and Commercialization of Anti-Cancer Therapeutics;
Grant number: A102059.; Grant sponsor: Ministry of Health, Welfare, and Family Affairs, Republic of Korea

*Correspondence to: Dr. Jin Cheon Kim, MD, Department of Surgery, University of Ulsan College of Medicine, 86 Asanbyeongwon-gil, Songpa-gu, Seoul 138-736, Korea. Fax: +82-247-490-27.
E-mail: jckim@amc.seoul.kr

Received 20 April 2013; Accepted 07 October 2013

DOI 10.1002/jso.23480

Published online 25 October 2013 in Wiley Online Library (wileyonlinelibrary.com).

opposite lobe) or intrahepatic dissemination (bilobar disease) requiring liver resection potentially jeopardizing postoperative liver function. Their clinicopatholgical findings included demography, pre-operative serum carcinoembryonic antigen (CEA) levels, primary diagnosis, co-morbidity, site of primary lesion, presence and location of pre-operative obstructions, tumor fixity to other structures, pathologic results, type and degree of distant metastasis, curability of the operation, post-operative complications and mortality, post-operative palliative treatment (chemotherapy and/or radiotherapy), and the type and treatment of recurrence. Histologically, tumors were classified as either low-grade (well-differentiated or moderately differentiated adenocarcinoma) or high-grade (poorly differentiated adenocarcinoma, or mucinous or signet-ring cell carcinoma).

Clinical, radiographic, and computer records were retrospectively reviewed. During chart review, additional data were gathered regarding the American Society of Anesthesiologists (ASA) score, Eastern Cooperative Oncology Group (ECOG) performance status and survival status using the national registry of medical insurance. The volumes of liver metastases were measured by a liver-specialty radiologist and scored as the percentage hepatic replacement (PHR) on portal phase CT scans [11]. PHR was measured by an intensity-based semi-automated method on a dedicated computer 3D workstation. Patients were divided into three groups according to the volume of liver metastasis: liver involvement of $\leq$25%, 26–50%, and >50% [12]. However, there was no survival difference between patients with liver involvement of 26–50% (n = 39, 11 months) and >50% (n = 27, 9 months, $P = 0.220$). Finally, patients were classified as limited liver metastasis (liver involvement $\leq$25%) or extensive liver metastasis (>25%). Major complications which required re-operation or hospitalization were also recorded. Operative mortality was defined as death that occurred during the hospital stay or within 30 days after surgery. Documentation of extra-abdominal metastasis was based on histological confirmation or radiological evidence. Symptomatic patients were limited to the patients who needed immediate intervention such as surgery, stent insertion, transfusion, and medication to control pain.

Operation

Decisions about first-line treatment were made by both colorectal surgeons and medical oncologists. The type of operation was decided by colorectal and liver surgeons taking into account the severity of disease (extent of metastasis, adjacent organ invasion) and patients' condition (age, performance status, and co-morbidity). As a multidisciplinary board was established in 2007, the decisions concerning most of study patients were not made by a multidisciplinary team. Palliative surgery was of two kinds depending on potential of the operation to cure: PR and NR. PR was defined as resection of the primary tumor without removal of liver metastatic lesions. NR included stoma construction and bypass surgery without removal of the primary tumor.

Chemotherapy

The use of chemotherapy, and the chemotherapy regimens applied were mainly decided by medical oncologists. Patients were considered to have undergone palliative chemotherapy if they completed at least two cycles of a course of chemotherapy following surgery. Eligibility criteria included ECOG performance status of 0 to 2, and age 75 years or less. Chemotherapy regimens were administered in accordance with the NCCN Clinical Practice Guidelines in Oncology (www.nccn.org).

Statistical Analysis

Patients' clinico-pathological parameters were evaluated as a function of the type of surgery received by cross-table analysis using Pearson's χ^2 test or Fischer's exact test, as indicated. Student's *t*-test was used for between-group comparisons of continuous variables. Clinical outcome was evaluated by overall survival (OS). Survival outcomes were compared using the Kaplan–Meier method with a log rank test, and potential prognostic variables were identified using Cox regression model.

To reduce the impact of treatment selection bias and potential confounding in this observational study, we performed rigorous adjustment for significant differences in characteristics of patients by propensity-score matching and the weighted Cox proportional-hazards regression models using the inverse-probability-of-treatment weighting (IPTW). Propensity scores were estimated by multiple logistic-regression analysis. To create a propensity score, all prespecified covariates were included in the full non-parsimonious models for operation group with PR versus NR. The discrimination and calibration abilities of each propensity score model were assessed by the C-statistic and the Hosmer–Lemeshow statistic. After all the propensity-score matches had been performed, we compared the baseline covariates between the two operation groups. Categorical variables were compared by McNemar's test. Statistical significance and the effect of operation group on outcomes were estimated using appropriate statistical methods for matched data. In the propensity-score-matched cohort, the risk of outcome was compared via a Cox regression model, with robust standard errors that accounted for the clustering of matched pairs. With the IPTW technique, weights for patients receiving PR were the inverse of (1-propensity score), and weights for patients receiving NR were the inverse of propensity score. All reported *P* values are two sided, and values of $P < 0.05$ were considered to indicate statistical significance. SPSS software version 18.0 (SPSS, Chicago, IL) and SAS software version 9.3 (SAS Institute, Inc, Cary, NC) were used for statistical analysis.

RESULTS

Patient and Tumor Characteristics

Table I shows the clinicopathological features of the 261 patients with unresectable colorectal liver metastases. Among the 113 patients (43%) who presented symptoms, the most frequent symptom was obstruction (n = 97), followed by anemia (n = 45), pain (n = 31), and others (n = 5). All of these symptoms were not different between PR and NR patients. NR patients received 55 stoma constructions (51 colostomies and 4 ileostomies) and 11 bypass surgery. Patients who underwent PR tended to be younger, with frequent colon tumors, infrequent adjacent organ invasion, better performance status, less involvement of liver metastases, and a higher rate of palliative chemotherapy than those with NR ($P < 0.001$–0.037, Table I).

Chemotherapy Regimens

Among the 48 patients who did not receive chemotherapy after palliative surgery, the most frequent reason was performance status deterioration (n = 26), followed by patients' refusal (n = 14), hold after first cycle of chemotherapy due to adverse effects (n = 4), postoperative mortality (n = 3), and prolonged postoperative complications (n = 1). First-line chemotherapy after palliative surgery consisted of irinotecan-containing regimens in 71 patients (33.3%), and oxaliplatin-containing regimens in 46 patients (21.6%), with a median number of 6 (range, 2–20) cycles per patients (Table II). Anti-vascular endothelial growth factor and anti-epidermal growth factor receptor were used more frequently in the PR group (n = 35) than in the NR group (n = 3, $P = 0.008$). However, no survival benefit was conferred on PR patients by chemotherapy using these targeted drugs.

Survival and Prognostic Factors

By the end of the study period, 250 patients (95.8%) had died. The 1-, 3-, and 5-year OS rates in patients with stage IV CRC were 65.5%,

TABLE I. Clinicopathological Characteristics

Variable	Total (n = 261)	PR (n = 195)	NR (n = 66)	*P* value
Gender, male	172 (65.9)	130 (66.7)	42 (63.6)	0.655
Age (years), mean ± SD	58.9 ± 11.3	58.6 ± 10.5	59.8 ± 13.5	0.429
≥70 years	43 (16.5)	24 (12.3)	19 (28.8)	0.001
Location, rectum	110 (42.1)	68 (34.9)	42 (63.6)	<0.001
CEA (ng/ml), mean ± SD	463 ± 1948.2	343 ± 1298.5	818 ± 3158.6	0.086
>6 ng/ml	193 (73.9)	139 (71.3)	54 (81.8)	0.106
Obstruction	97 (37.2)	70 (35.9)	27 (40.9)	0.466
ASA score, >2	23 (8.8)	16 (8.2)	7 (10.6)	0.616
Adjacent organ invasion	36 (13.8)	19 (9.7)	17 (25.8)	0.001
ECOG performance status >2	22 (8.4)	12 (6.2)	10 (15.2)	0.037
Liver metastasis >25%	66 (25.3)	43 (22.1)	23 (34.8)	0.049
Complication	15 (5.7)	9 (4.6)	6 (9.1)	0.219
Mortality	3 (1.1)	1 (0.5)	2 (3.0)	0.158
Chemotherapy	213 (81.6)	166 (85.1)	47 (71.2)	0.016

SD, standard deviation; PR, palliative resection; NR, non-resection; CEA, carcinoembryonic antigen; ASA, American Society of Anesthesiologists; ECOG, Eastern Cooperative Oncology Group.

17.2%, and 5.5%, respectively. Median survival was 18 months for all patients, 21 months in PR patients, and 10 months in NR patients ($P < 0.001$, Fig. 1A). Among the variables examined, serum CEA >6 ng/ml, ECOG performance status >2, adjacent organ invasion, liver metastasis >25%, NR, and absence of chemotherapy were independent prognostic factors in multivariate analysis ($P < 0.001$–0.014, Table III).

Because the demographic data differed between PR and NR patients, we subsequently matched 51 pairs of cases by propensity-score matching analysis to reduce comparison bias (Table IV). The discrimination and calibration abilities of the propensity score model were 0.831 by the C-statistic and $P = 0.512$ by the Hosmer–Lemeshow statistic, respectively. PR patients had better survivals than NR patients in various multivariate analyses, including propensity-score matching (Fig. 1B) and IPTW (Table V).

TABLE II. Chemotherapy Regimens after Palliative Surgery

	Palliative resection	Non-resection
Line 1	n = 166	n = 47
Routine protocols, n (%)	160 (96.4)	47 (100)
FL	28	6
FOLFOX	24	6
FOLFIRI	38	15
Oral capecitabine	44	12
XELOX	13	3
XELIRI	13	5
Routine protocols and biotherapies, n (%)	6 (3.6)	0
Anti-VEGF	3	0
Anti-EGFR	3	0
Line 2	n = 108	n = 27
Routine protocols, n (%)	96 (88.9)	26 (96.3)
FL	0	0
FOLFOX	47	16
FOLFIRI	25	3
Oral capecitabine	5	1
XELOX	15	6
XELIRI	4	0
Routine protocols and biotherapies, n (%)	10 (9.3)	1 (3.7)
Anti-VEGF	5	0
Anti-EGFR	5	1
Biotherapy alone, n (%)	2 (1.8)	0

FL, 5-fluorouracil + leucovorin; FOLFOX, FL + oxaliplatin; FOLFIRI, FL + irinotecan; XELOX, oral capecitabine + oxaliplatin; XELIRI, oral capecitabine + irinotecan; VEGF, vascular endothelial growth factor; EGFR, epidermal growth factor receptor.

Differences in Survival between PR and NR Patients According to the Extent of Liver Metastasis

Among the patients with limited liver metastases (volume ≤ 25%), NR patients (n = 43) had poorer survival than PR patients (n = 152) in multivariate analysis [hazard ratio (HR): 2.183, 95% confidence interval (CI): 1.401–3.402; $P = 0.001$, Fig. 2A]. However, there was no significant difference between NR and PR patients in cases of extensive liver metastasis (volume > 25%) [HR: 1.560, 95% CI: 0.860–2.830; $P = 0.143$, Fig. 2B]. At the end of the study period, 11 patients (4.2%) survived (range: 42–158 months). All of these survivors were below 70 years and had limited liver metastases, good ECOG performance status, and received PR and chemotherapy.

DISCUSSION

Many studies of various issues in the management of stage IV CRC are reported annually [8,12–16]. The current study aimed to identify the most appropriate surgical treatment for stage IV CRC using a relatively large continuous cohort at a single tertiary institution. It was based on the assumption that the type of surgery used as first-line treatment would be the most important prognostic factor for survival in CRC patients with unresectable liver metastasis. In addition, we aimed to establish guidelines for choosing the type of palliative surgery based on the extent of metastasis.

To date, the effect of surgical resection versus chemotherapy alone on the survival of patients with unresectable stage IV CRC remains controversial [2,4,12]. A recent meta-analysis of 1,062 patients showed that patients who received PR of the primary tumor had a survival advantage of 6 months over patients who received chemotherapy alone [17]. In the present study, the survival benefit of receiving PR rather than NR was as much as 10 months. While neither NR nor chemotherapy alone result in removal of the primary tumor, patients with NR had poorer clinical findings, including increased incidence of obstruction, later initiation of chemotherapy, and a higher risk of morbidity and mortality related to surgery than patients treated with chemotherapy alone [2,18]. This may explain why the survival difference between PR and NR was greater than between PR and chemotherapy alone. Some authors have suggested that debulking of the primary tumor improves the response to chemotherapy, as previously

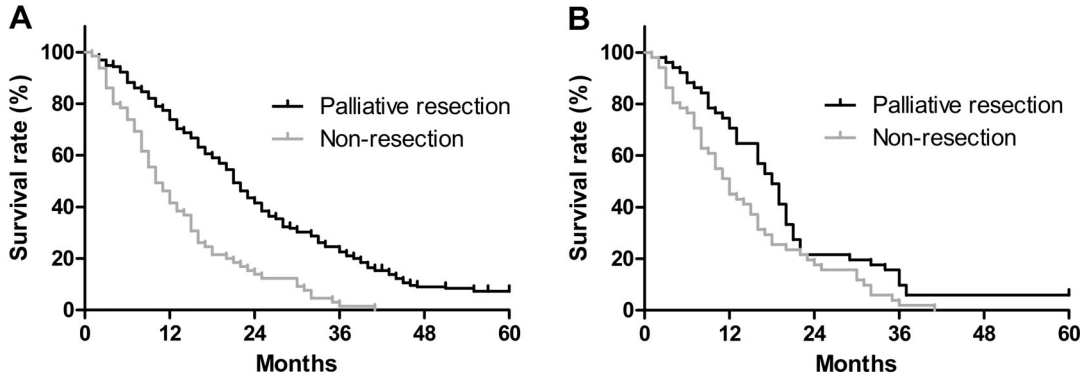

Fig. 1. Survival curves according to type of surgery in patients with unresectable colorectal liver metastases. **A**: All patients without adjustment (n = 261, $P < 0.001$). **B**: Propensity-score matched pairs (n = 102, $P = 0.048$).

demonstrated for advanced renal cell and ovarian cancers [12,17]. Moreover, surgical removal of the primary tumor confers the acquired immunity advantage of reversing immune suppression even in the presence of extensive metastatic disease [19].

The present study has the potential value of suggesting guidelines for choosing the type of operation (resection or not) in symptomatic patients with unresectable stage IV CRC. Up to 65% of stage IV CRC patients had symptoms of tumor complications such as intestinal obstruction, perforation, intractable pain, and bleeding [10]. The most common symptom of patients with stage IV CRC is intestinal obstruction with rates of 7% to 29% [20,21] Because of the more advanced status of the patients in our study, we observed a higher incidence (37.2%) of intestinal obstruction. Non-operative methods including endoscopic stenting or laser recanalization have generally been advocated for patients with poor performance status and/or advanced age in order to reduce the morbidity and mortality associated with surgery. However,

TABLE III. Prognostic Factors

	Univariate analysis				Multivariate analysis[a]		
	n	HR	95% CI	*P* value	HR	95% CI	*P* value
Gender							
Female	89	1					
Male	172	0.858	0.660–1.116	0.253			
Age							
<70 years	218	1					
≥70 years	43	2.006	1.434–2.807	<0.001			
Location							
Colon	151	1					
Rectum	110	0.845	0.657–1.087	0.189			
CEA							
≤6 ng/ml	68	1			1		
>6 ng/ml	193	1.515	1.132–2.028	0.005	1.474	1.081–2.011	0.014
ASA							
1–2	238	1					
3–4	23	1.624	1.046–2.522	0.030			
ECOG performance status							
0–2	239	1			1		
3–4	22	10.854	6.622–17.79	<0.001	3.399	1.902–6.076	<0.001
Adjacent organ invasion							
No	225	1			1		
Yes	36	1.979	1.385–2.828	<0.001	1.718	1.174–2.513	0.005
Liver metastasis							
≤25%	195	1			1		
>25%	66	2.555	1.905–3.426	<0.001	2.348	1.730–3.187	<0.001
Type of operation							
Palliative resection	195	1			1		
Non-resection	66	2.532	1.886–3.398	<0.001	1.877	1.379–2.555	<0.001
Chemotherapy							
No	48	1			1		
Yes	213	0.201	0.144–0.279	<0.001	0.243	0.160–0.369	<0.001

HR, Hazard ratio; CI, confidence interval; CEA, carcinoembryonic antigen; ASA, American Society of Anesthesiologists.
[a]Cox proportional hazards model was applied with backward elimination.

TABLE IV. Comparison of Characteristics after Propensity-Score Correction

Variable	Total (n = 102)	PR (n = 51)	NR (n = 51)	*P* value*
Gender, male	61 (59.8)	30 (58.9)	31 (60.8)	0.827
Age ≥70 years	24(23.5)	9(17.7)	15(29.4)	0.109
Location, rectum	62(60.8)	29(56.9)	33(64.7)	0.346
CEA >6 ng/ml	87(85.3)	46(90.2)	41(80.4)	0.132
ASA score, >2	8(7.8)	4(7.8)	4(7.8)	0.999
Adjacent organ invasion	23(22.5)	13(25.5)	10(19.6)	0.366
Liver metastasis >25%	28 (27.5)	15 (29.4)	13 (25.5)	0.617

CEA, Carcinoembryonic antigen; ASA, American Society of Anesthesiologists.
*P value after PS matching were evaluated by McNemar's test.

TABLE V. Multivariate Analyses of Survival Outcomes for Palliative Resection of Primary Tumor

Model	n	HR (95% CI)	*P* value
Propensity-score matching[a]	102	1.481 (1.003–2.185)	0.048
IPTW model[b]	261	2.357 (1.700–3.268)	<0.001

HR, Hazard ratio; CI, confidence interval; IPTW, inverse-probability-of-treatment weighting.
HRs are for the non-resection (NR) group as compared with palliative resection (PR) group.
[a]A Cox proportional hazards model was applied by using propensity score-based matching with robust standard errors and adjusted by "ECOG performance status" and "Chemotherapy."
[b]A Cox proportional hazards model using IPTW was applied and adjusted by "ECOG performance status" and "Chemotherapy."

some patients undergoing these procedures suffer complications such as perforation, bleeding, stent migration, and re-obstruction [22]. In terms of controlling symptoms, our institution has favored PR in patients with unresectable metastatic CRC.

A recent study found that the mortality rate of palliative surgery had decreased from 10.6% to 2.7% in 20 years (1989–2009), due to advances in anesthesiological and surgical techniques [23]. The overall mortality of our patients with unresectable liver metastases was slightly lower (1.1%) than the 1.7–9.2% reported previously [10,13,16,17]. Although NR resulted in higher mortality rates than PR in previous reports [9,24], we found no significant difference in mortality and complication rates between our NR and PR patients. Several studies have identified predictors of morbidity and mortality, including extensive co-morbidities, old age (≥70 years), adjacent organ invasion, extra-hepatic metastases, and a volume of liver involvement >50% [13,16]. Most of these predictors were closely associated with NR in the present study.

Liver tumor burden has been shown in many studies to be a critical prognostic factor, when the degree of liver metastasis is evaluated based on the proportion of tumor involvement, the number of deposits, tumor size, and tumor distribution [15,25–27]. Of these variables, we evaluated only liver tumor burden by volume, which can be used to evaluate the extent of liver metastasis objectively and to easily assess the resectability of liver metastases in the clinical situation. Although a few studies define extensive liver metastasis as volume of liver involvement >50% [12,15,28], we defined involvement >25% as extensive liver metastasis in those of our patients who underwent palliative surgery. We found that a survival benefit for patients who underwent resection of primary tumor was particularly evident in those with limited (≤25%) rather than extensive (>25%) liver metastasis. However, the type of palliative surgery should be determined in consideration of all proven prognostic factors including performance status, extent of metastasis, and adjacent organ invasion. In the rare conditions such as massive bleeding or perforation, resection of primary tumor should be performed regardless of the severity of disease or patient's condition. When there is an extensive liver metastasis (>25%) and a safe resection of the primary tumor is feasible in symptomatic patients, resection of primary tumor is preferable option.

Both propensity score matching and IPTW estimation are tools for causal inference in non-randomized studies, which allow for conditioning on large sets of covariates [29]. Propensity score methods offer a principled approach to deal with this type of confounding bias. Through efficient matching, covariates are balanced, and their confounding effect can be minimized or entirely removed. IPTW estimation requires that the analyst specify a model of the treatment rather than the outcome. If the treatment model is correctly specified, the reweighting results in a population of patients in whom treatment assignment is unrelated to the baseline variables that are

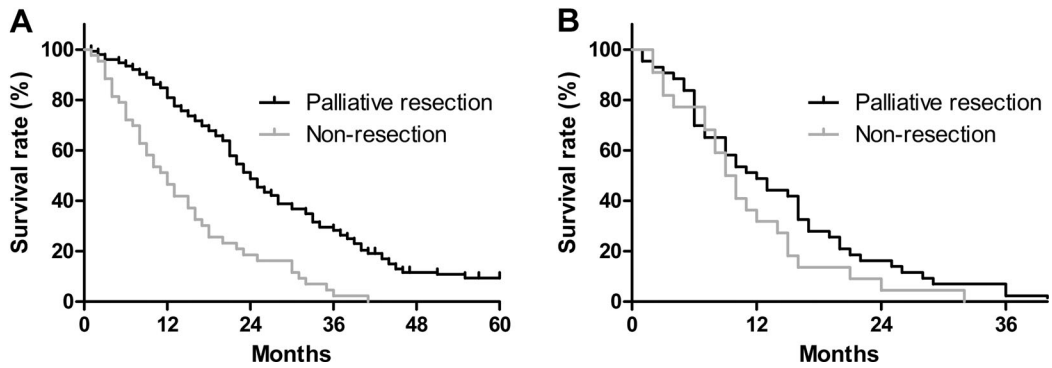

Fig. 2. Survival curves according to type of surgery in patients with unresectable colorectal liver metastases. **A**: Patients with limited liver metastasis (volume involvement ≤25%, $P = 0.001$). **B**: Patients with extensive liver metastasis (volume involvement >25%, $P = 0.143$).

included in the treatment model. The IPTW approach attempts to mimic a situation in which treatment is randomly allocated to individuals [30].

This study is limited by its retrospective design. Propensity scores can only adjust for observed confounders not for unobserved confounders. Numerous factors may influence survival after surgery and it is difficult to deal with them all at the same time. Thus, our propensity score matching and IPTW models will not eliminate all selection bias. Although the present kind of study is difficult to conduct prospectively, the true benefit of primary tumor resection should be established in large prospective randomized trials.

In conclusion, PR results in better survival when the patient's overall condition permits an aggressive approach. Palliative resection appears to increase survival compared with NR in patients with limited liver metastases, but possibly not in those with extensive liver metastases.

ACKNOWLEDGMENTS

This study was supported by grants (to J.C. Kim) from the Asan Institute for Life Sciences (2013-069 and 9-490), the Korea Health 21 R&D Project (A062254), and the Center for Development and Commercialization of Anti-Cancer Therapeutics (A102059), Ministry of Health, Welfare, and Family Affairs, Republic of Korea.

REFERENCES

1. Cook AD, Single R, McCahill LE: Surgical resection of primary tumors in patients who present with stage IV colorectal cancer: An analysis of surveillance, epidemiology, and end results data, 1988 to 2000. Ann Surg Oncol 2005;12:637–645.
2. Damjanov N, Weiss J, Haller DG: Resection of the primary colorectal cancer is not necessary in nonobstructed patients with metastatic disease. Oncologist 2009;14:963–969.
3. Gallagher DJ, Kemeny N: Metastatic colorectal cancer: From improved survival to potential cure. Oncology 2010;78:237–248.
4. Benoist S, Pautrat K, Mitry E, et al.: Treatment strategy for patients with colorectal cancer and synchronous irresectable liver metastases. Br J Surg 2005;92:1155–1160.
5. Tebbutt NC, Norman AR, Cunningham D, et al.: Intestinal complications after chemotherapy for patients with unresected primary colorectal cancer and synchronous metastases. Gut 2003;52:568–573.
6. Gruenberger B, Tamandl D, Schueller J, et al.: Bevacizumab, capecitabine, and oxaliplatin as neoadjuvant therapy for patients with potentially curable metastatic colorectal cancer. J Clin Oncol 2008;26:1830–1835.
7. Reddy SK, Tsung A, Marsh JW, et al.: Does neoadjuvant chemotherapy reveal disease precluding surgical treatment of initially resectable colorectal cancer liver metastases? J Surg Oncol 2012;105:55–59.
8. Mik M, Dziki L, Galbfach P, et al.: Resection of the primary tumour or other palliative procedures in incurable stage IV colorectal cancer patients? Colorectal Dis 2010;12:e61–e67.
9. Law WL, Chan WF, Lee YM, et al.: Non-curative surgery for colorectal cancer: Critical appraisal of outcomes. Int J Colorectal Dis 2004;19:197–202.
10. Yun HR, Lee WY, Lee WS, et al.: The prognostic factors of stage IV colorectal cancer and assessment of proper treatment according to the patient's status. Int J Colorectal Dis 2007;22:1301–1310.
11. Purkiss SF: The assessment of percentage hepatic replacement using planimetry of computerized tomographic images. Surg Oncol 1996;5:231–236.
12. Galizia G, Lieto E, Orditura M, et al.: First-line chemotherapy vs bowel tumor resection plus chemotherapy for patients with unresectable synchronous colorectal hepatic metastases. Arch Surg 2008;143:352–358;discussion 358.
13. Kleespies A, Fuessl KE, Seeliger H, et al.: Determinants of morbidity and survival after elective non-curative resection of stage IV colon and rectal cancer. Int J Colorectal Dis 2009;24:1097–1109.
14. Kobayashi H, Kotake K, Sugihara K: Prognostic scoring system for stage IV colorectal cancer: Is the AJCC sub-classification of stage IV colorectal cancer appropriate? Int J Clin Oncol 2013;18:696–703.
15. Konyalian VR, Rosing DK, Haukoos JS, et al.: The role of primary tumour resection in patients with stage IV colorectal cancer. Colorectal Dis 2007;9:430–437.
16. Stillwell AP, Buettner PG, Siu SK, et al.: Predictors of postoperative mortality, morbidity, and long-term survival after palliative resection in patients with colorectal cancer. Dis Colon Rectum 2011;54:535–544.
17. Stillwell AP, Buettner PG, Ho YH: Meta-analysis of survival of patients with stage IV colorectal cancer managed with surgical resection versus chemotherapy alone. World J Surg 2010;34:797–807.
18. Karoui M, Roudot-Thoraval F, Mesli F, et al.: Primary colectomy in patients with stage IV colon cancer and unresectable distant metastases improves overall survival: Results of a multicentric study. Dis Colon Rectum 2011;54:930–938.
19. Danna EA, Sinha P, Gilbert M, et al.: Surgical removal of primary tumor reverses tumor-induced immunosuppression despite the presence of metastatic disease. Cancer Res 2004;64:2205–2211.
20. Wang HS, Lin JK, Mou CY, et al.: Long-term prognosis of patients with obstructing carcinoma of the right colon. Am J Surg 2004;187:497–500.
21. Winner M, Mooney SJ, Hershman DL, et al.: Management and outcomes of bowel obstruction in patients with stage IV colon cancer: A population-based cohort study. Dis Colon Rectum 2013;56:834–843.
22. Wasserberg N, Kaufman HS: Palliation of colorectal cancer. Surg Oncol 2007;16:299–310.
23. Platell C, Ng S, O'Bichere A, et al.: Changing management and survival in patients with stage IV colorectal cancer. Dis Colon Rectum 2011;54:214–219.
24. Makela J, Haukipuro K, Laitinen S, Kairaluoma MI: Palliative operations for colorectal cancer. Dis Colon Rectum 1990;33:846–850.
25. Yamamura T, Tsukikawa S, Akaishi O, et al.: Multivariate analysis of the prognostic factors of patients with unresectable synchronous liver metastases from colorectal cancer. Dis Colon Rectum 1997;40:1425–1429.
26. Sakamoto Y, Fujita S, Akasu T, et al.: Is surgical resection justified for stage IV colorectal cancer patients having bilobar hepatic metastases?—An analysis of survival of 77 patients undergoing hepatectomy. J Surg Oncol 2010;102:784–788.
27. Chafai N, Chan CL, Bokey EL, et al.: What factors influence survival in patients with unresected synchronous liver metastases after resection of colorectal cancer? Colorectal Dis 2005;7:176–181.
28. Liu SK, Church JM, Lavery IC, et al.: Operation in patients with incurable colon cancer—Is it worthwhile? Dis Colon Rectum 1997;40:11–14.
29. Stuart EA: Matching methods for causal inference: A review and a look forward. Stat Sci 2010;25:1–21.
30. Suarez D, Haro JM, Novick D, et al.: Marginal structural models might overcome confounding when analyzing multiple treatment effects in observational studies. J Clin Epidemiol 2008;61:525–530.