Obesity Significantly Affects the Incidence of Hepatic Injury in Patients with Colorectal Liver Metastasis

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ABSTRACT

Objective: Surgical resection is the mainstay treatment for colorectal liver metastasis. In unresectable cases, chemotherapy is used to transform the tumor into resectable lesions, with related concerns about toxicity to non-tumoral liver parenchyma. Liver toxicity, including steatosis, steatohepatitis, and sinusoidal dilation, has been reported. However, these changes are difficult to histologically distinguish from non-alcoholic fatty liver disease, which is commonly found in populations and attributed mainly to metabolic syndrome. The aim of this study was to investigate the factors associated with liver injury in patients with colorectal liver metastasis.

Methods: This retrospective study included the patients who underwent hepatic resection for colorectal liver metastasis at Siriraj Hospital during the eight-year period (2006 to 2013). Patient demographic data, clinical characteristics, and histologic changes related to liver injury were collected and analyzed. Ten factors were evaluated for association with liver injury in selected patients.

Results: Ninety-two patients (50 men, 42 women) were included, with a mean age of 59.4 years (range: 48.5-70.3). Forty-four patients (47.8%) received preoperative chemotherapy (CMT). Incidence of liver injury was not significantly different between the CMT and non-CMT groups (65.9% vs. 62.5%; p=0.902). However, incidence of liver injury was significantly higher in obese patients than in non-obese patients (82.8% vs. 55.6%; p=0.022, odds ratio=3.95). Multivariate analysis showed that obesity (BMI >25 kg/m^2) was the only factor significantly associated with liver injury in patients with colorectal liver metastasis.

Conclusion: Of the ten factors evaluated, obesity was the only factor found to be significantly associated with liver injury in patients with colorectal liver metastasis.

Keywords: Obesity; hepatic injury; colorectal liver metastasis (Siriraj Med J 2018;70: 429-437)

INTRODUCTION

Colorectal carcinoma is the third most common cancer in men and the second in women worldwide.[1] According to the National Cancer Institute and a population-based cancer registry in Thailand, colorectal carcinoma is the third most common cancer among males after liver cancer and lung cancer, and the fifth after cancer of the breast, cervix, liver and lung among females.[2] A search of the database at our center (Siriraj Hospital) revealed colorectal carcinoma to be the third and second most common cancer in males and females, respectively.[3] The most common site of distant metastasis is the liver.

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Current management of colorectal liver metastasis requires a multidisciplinary approach, with combination therapy consisting of complete surgical resection and systemic chemotherapy offering the best opportunity for prolonged survival. However, there are, only a small percentage of patients that are eligible for upfront resection. For patients with initially unresectable metastasis, preoperative chemotherapy may transform the tumor into a resectable lesion.[4] However, chemotherapy may adversely affect non-tumoral areas of the liver parenchyma. Different patterns of liver injury are attributed to different types of chemotherapy. By way of example, fluorouracil can cause steatosis, oxaliplatin can cause steatosis and sinusoidal dilation, and irinotecan can cause steatosis and steatohepatitis.[4-8] Many studies have reported that chemotherapy-induced liver injuries cause increased perioperative morbidities and mortality.[9-12] In contrast, some other studies reported that chemotherapy-induced liver injuries had no effect on clinical outcomes.[13-16] Conflicting results among studies were attributed to differences in duration and number of cycles, and interval time before surgery.[5-7]

Chemotherapy-induced liver injury cannot be distinguished histologically from nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH). NAFLD and NASH are associated with obesity and metabolic syndrome, both of which are now very common in many, if not most, populations.[17] According to the Fourth National Health Examination Survey (2008-2009) conducted by the Thailand National Health Examination Survey Office (NHESO), the rate of obesity in Thailand (BMI ≥25 kg/m^2) is 28.3% among male adults and 40.7% among female adults.[18]

A finding of liver injury among patients with colorectal liver metastasis is relatively common in routine pathology practice. Accordingly, the aim of this study was to investigate the factors associated with liver injury in patients with colorectal liver metastasis.

MATERIALS AND METHODS

This retrospective study included patients with colorectal liver metastasis who underwent hepatic resection at Siriraj Hospital during the 2006 to 2013 study period that were identified from the electronic database of the Department of Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University using the keywords *liver* and *adenocarcinoma*. Siriraj Hospital is located in Bangkok, and is Thailand's largest national tertiary referral center. The protocol for this study was approved by the Siriraj Institutional Review Board (Si 552/2014).

The following demographic and clinical data were collected: age; gender; underlying diseases, including diabetes mellitus (DM), hypertension (HT), dyslipidemia (DLP), ischemic heart disease (IHD), hepatitis B virus (HBV) infection, and hepatitis C virus (HCV) infection, history of preoperative chemotherapy (CMT), and, height and weight. Obesity in this study was defined as body mass index (BMI) >25 kg/m^2 (Asian adults).[19] Patients having one or more of the following were excluded: 1) greater than 1 year interval between the last cycle of chemotherapy and hepatic surgery; 2) change in chemotherapy regimen during treatment; 3) incomplete chemotherapy treatment information; 4) received other treatment prior to the current preoperative chemotherapy, including other course of chemotherapy, transcatheter arterial chemoembolization, portal vein embolization, and radiofrequency ablation.

Histologic changes in non-tumoral liver parenchyma, including steatosis, steatohepatitis, sinusoidal dilation, fibrosis, and nodular regenerative hyperplasia, were retrospectively reviewed by a pathologist who was blinded to patient clinical data. The pathologist reviewed all available H&E-stained slides and Masson trichrome-stained slides of non-tumoral liver parenchyma. Cases with inadequate liver parenchymal area for evaluation (less than 1 cm^2) were excluded.

Fatty change was evaluated based on the NASH Clinical Research Network Scoring System for Nonalcoholic Fatty Liver Disease.[20] Steatosis was diagnosed when >5% of the liver parenchyma was involved by fat. Steatohepatitis was diagnosed when steatosis, fibrosis, lobular inflammation, and hepatocellular ballooning degeneration were simultaneously present. Fibrosis stage was evaluated using the METAVIR scoring system.[21] Stage 2-4 fibrosis was considered advanced fibrosis. Sinusoidal dilation was recorded for scores >1 according to the Rubbia-Brandt grading system.[22] A patient was regarded as having liver injury if steatosis, steatohepatitis, or sinusoidal dilation was observed by microscopic evaluation.

Statistical analysis

Aloysius, *et al.*, reported that steatosis was found in 68% of patients receiving combined fluorouracil and oxaliplatin for colorectal liver metastasis, as compared with 20% in patients that did not receive chemotherapy.[23] The required sample size was calculated based on two estimated proportions of two groups method, with a 95% confidence interval (CI) and a 5% error. This calculation resulted in a required sample size of 16 patients.

Bower, *et al.*, found that 39% of obese patients (BMI ≥30 kg/m^2) had steatosis or steatohepatitis, as compared with a rate of 12.8% in non-obese patients.[24] The required

sample size from the same method was 43 patients.

Continuous data are described as mean ± standard deviation (SD), mean and range, or median and range, as appropriate. Number and percentage were used to express categorical data. Mann-Whitney U test or independent t-test was used to compare continuous data between groups. Categorical data were compared using chi-square test or Fisher's exact test. Factors of interest and factors with a *p*-value less than 0.1 in univariate analysis were entered into multiple logistic regression analysis. Data were prepared and analyzed using PASW Statistics version 18.0 (SPSS, Inc., Chicago, IL, USA). All tests of significance were two-tailed, and a *p*-value less than 0.05 was considered to be statistically significant.

RESULTS

During the 2006 to 2013 study period, 163 patients were diagnosed with colorectal liver metastasis from hepatic resection at our center. Sixty cases and 11 eleven cases were excluded for not meeting non-pathologic and pathologic inclusion criteria, respectively (Fig 1). The remaining 92 patients were included.

Mean age of patients was 59.4 years (range: 48.5-70.3). Seventy-six patients (82.6%) were aged older than 50 years, and 50 patients (54.3%) were male. Forty-eight patients (52.2%) had underlying disease(s), as described in Table 1. Twenty-nine patients (31.5%) were obese. Forty-four patients (47.8%) received preoperative chemotherapy (CMT), and the remaining 48 patients (52.2%) did not receive preoperative chemotherapy (non-CMT) (Table 1).

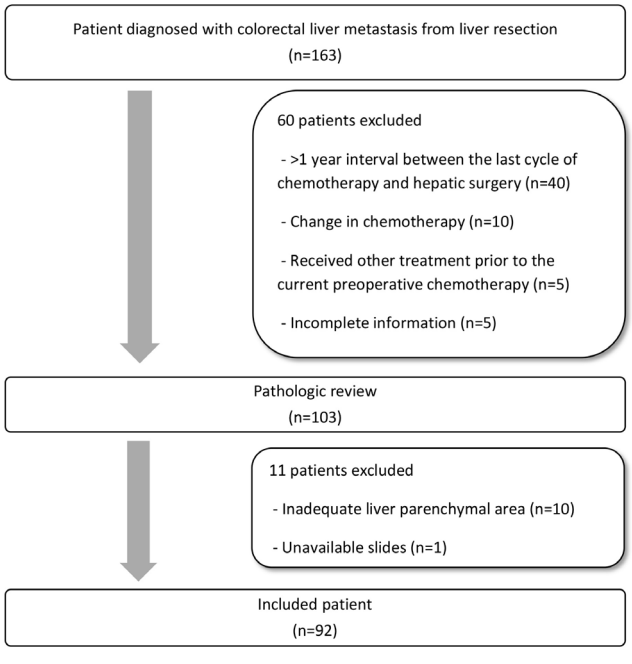

Fig 1. CONSORT flow diagram.

Association between obesity/CMT status and other clinical factors

Association between obesity/CMT status and other clinical factors was evaluated by Fisher's exact test. The other clinical factors included age, gender, and presence of underlying disease(s) (i.e., DM, HT, DLP, IHD, HBV, and HCV). Twenty-nine patients (31.5%) were obese (BMI ≥25 kg/m^2) (Table 2). Incidence of diabetes mellitus was significantly higher in obese patients than in non-obese patients (41.4% vs. 9.5%; p=0.001) (Table 2).

Preoperative chemotherapy regimen

Among the group of patients that received preoperative chemotherapy (CMT), fluorouracil or capecitabine combined with oxaliplatin was the most common regimen, followed by fluorouracil or capecitabine alone, and fluorouracil or capecitabine combined with irinotecan (Table 3). The mean duration of treatment was 4.4±1.4 months. The median number of cycles was 6 (range: 3-14). The mean interval between the last cycle of chemotherapy and liver resection was 2.3 months (range: 0.1-11.4).

Fifty-nine patients (64.1%) had liver injury, which was defined as presence of steatosis (Fig 1-3), steatohepatitis, or sinusoidal dilation (Table 4). Forty-one patients (44.6%) had steatosis, 9 patients (9.8%) had steatohepatitis, and 33 patients (35.9%) had sinusoidal dilation. Advanced fibrosis was found in 5 patients (5.4%), and nodular regenerative hyperplasia was observed in 8 patients (8.7%).

Incidence of liver injury was not significantly different between the CMT group and the non-CMT group (65.9% vs. 62.5%; p=0.902). However, incidence of liver injury was significantly higher in obese patients than in non-obese patients (82.8% vs. 55.6%; p=0.022). Steatosis, steatohepatitis, and fibrosis were significantly more commonly found in obese patients than in non-obese patients (79.3% vs. 28.6%, p<0.001; 24.1% vs. 3.2%, p=0.004; and, 17.2% vs. 0%, p=0.002, respectively) (Table 5).

Of the 10 factors included in univariate analysis, only obesity was found to be significantly associated with liver injury in patients with colorectal liver metastasis (p=0.015, odds ratio=3.84) (Table 6). Of the 4 factors of interest and the 1 factor that emerged from univariate analysis (age, DM, HT, preoperative CMT, and obesity, respectively), only obesity was once again found to be significantly associated with liver injury in our study population (p=0.022, odds ratio=3.95) (Table 6).

TABLE 1. Demographic and clinical characteristics of patients diagnosed with colorectal liver metastasis.

Characteristics	n (%)
Patients	92 (100%)
Age (years), mean (range)	59.4 (48.5-70.3)
Age ≤50 years	16 (17.4%)
Age >50 years	76 (82.6%)
Gender	
Male	50 (54.3%)
Female	42 (45.7%)
Underlying disease	
DM	18 (19.6%)
HT	39 (42.4%)
DLP	20 (21.7%)
IHD	7 (7.6%)
HBV infection	4 (4.3%)
HCV infection	1 (1.1%)
BMI (mg/m^2), mean (range)	23.9 (20.4-27.4)
Non-obese (BMI <25 mg/m^2)	63 (68.5%)
Obese (BMI ≥25 mg/m^2)	29 (31.5%)
Preoperative CMT	
No	48 (52.2%)
Yes	44 (47.8%)

Abbreviations: DM, diabetes mellitus; HT, hypertension; DLP, dyslipidemia; IHD, ischemic heart disease; HBV, hepatitis B virus; HCV, hepatitis C virus; BMI, body mass index; CMT, chemotherapy

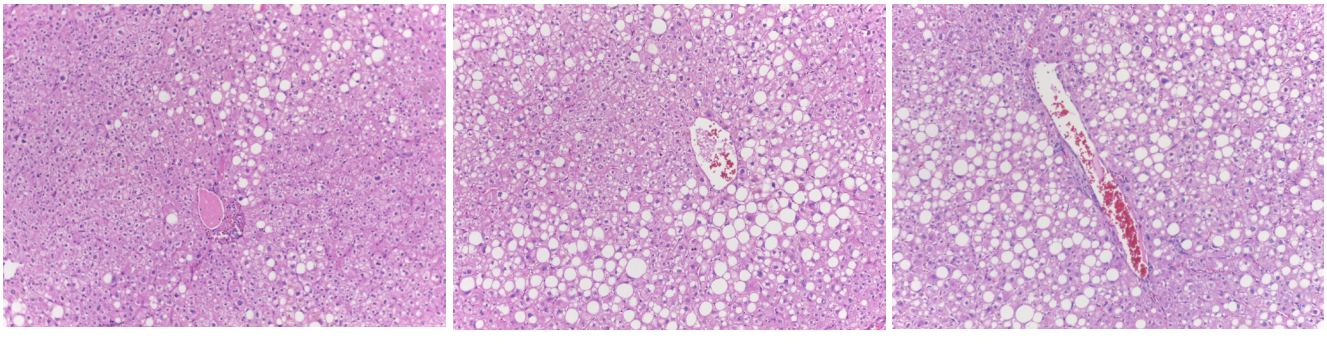

Fig 2-4: Hepatocytes show varying degree of steatosis from mild (fig 2), moderate (fig 3) and severe (fig 4). Steatosis shows characteristics large macrovesicular globules within cytoplasm of hepatocytes pushing the nuclei to the periphery.

TABLE 2. Obesity and chemotherapy status relative to other clinical factors in patients diagnosed with colorectal liver metastasis.

Characteristic	Non-CMT (n=48)	CMT (n=44)	*p*-value	Non-obese (n=63)	Obese (n=29)	*p*-value
Age (years)	61.5±9.7	57.1±11.8	0.052	59.1±10.4	60.6±12.0	0.557
Age ≤50 years	7 (14.6%)	9 (20.5%)	0.641	11 (17.5%)	5 (17.2%)	1.000
Age >50 years	41 (85.4%)	35 (79.5%)		52 (82.5%)	24 (82.8%)	
Gender						
Male	25 (52.1%)	25 (56.8%)	0.806	32 (50.8%)	18 (62.1%)	0.433
Female						
Underlying disease						
DM	11 (22.9%)	7 (15.9%)	0.560	6 (9.5%)	12 (41.4%)	0.001*
HT	23 (47.9%)	16 (36.4%)	0.363	22 (34.9%)	17 (58.6%)	0.056
DLP	14 (29.2%)	6 (13.6%)	0.121	11 (17.5%)	9 (31.0%)	0.232
IHD	3 (6.3%)	4 (9.1%)	0.706	4 (6.3%)	3 (10.3%)	0.674
HBV infection	2 (4.2%)	2(4.5%)	1.000	2 (3.2%)	2 (6.9%)	0.588
HCV infection	1 (2.3%)	0 (0.0%)	0.478	1 (1.6%)	0 (0.0%)	1.000
BMI (mg/m^2)	24.3±3.8	23.3±3.2	0.178	NA	NA	
Obese (BMI<25 mg/m^2)	19 (39.6%)	10 (22.7%)	0.130	NA	NA	
Non-obese (BMI ≥25 mg/m^2)	29 (60.4%)	34 (77.3%)		NA	NA	
Preoperative CMT						
Yes	NA	NA		34 (54.0%)	10 (34.5%)	0.130
No	NA	NA		29 (46.0%)	19 (65.5%)	

Data presented as number and percentage or mean ± standard deviation
*A *p*-value<0.05 indicates statistical significance
Abbreviations: CMT, chemotherapy; DM, diabetes mellitus; HT, hypertension; DLP, dyslipidemia; IHD, ischemic heart disease; HBV, hepatitis B virus; HCV, hepatitis C virus; BMI, body mass index

TABLE 3. Number of colorectal liver metastasis patients receiving each chemotherapy regimen.

Chemotherapy regimen	n (%)
Fluorouracil or capecitabine	15 (34.1%)
Fluorouracil or capecitabine + oxaliplatin	24 (54.5%)
Fluorouracil + irinotecan	5 (11.4%)

TABLE 4. Pathologic change of the liver in patients diagnosed with colorectal liver metastasis.

Type of pathologic change	n (%)
Liver injury	59/92 (64.1%)
Steatosis	41/59 (69.5%)
Steatohepatitis	9/59 (15.3%)
Sinusoidal dilatation	33/59 (55.9%)
Advanced fibrosis	5/92 (5.4%)
Nodular regenerative hyperplasia	8/92 (8.7%)

TABLE 5. Comparison of pathologic changes of the liver between the non-CMT/CMT and non-obese/obese groups.

Type of pathologic change	Non-CMT (n=48)	CMT (n=44)	*p*-value	Non-obese (n=63)	Obese (n=29)	*p*-value
Liver injury	30 (62.5%)	29 (65.9%)	0.902	35 (55.6%)	24 (82.8%)	0.022*
Steatosis	25 (52.1%)	16 (36.4%)	0.192	18 (28.6%)	23 (79.3%)	<0.001*
Steatohepatitis	4 (8.3%)	5 (11.4%)	0.732	2 (3.2%)	7 (24.1%)	0.004*
Sinusoidal dilatation	14 (29.2%)	19 (43.2%)	0.237	24 (38.1%)	9 (31.0%)	0.673
Advanced fibrosis	3 (6.3%)	2 (4.5%)	1.000	0 (0.0%)	5 (17.2%)	0.002*
Nodular regenerative hyperplasia	1 (2.1%)	7 (15.9%)	0.026*	6 (9.5%)	2 (6.9%)	1.000

Data presented as number and percentage
*A *p*-value<0.05 indicates statistical significance
Abbreviation: CMT, chemotherapy

CONCLUSION

In patients with unresectable colorectal liver metastasis, neoadjuvant chemotherapy can suitably reduce the size of the tumor to facilitate surgical resection.[4-6] In resectable cases, perioperative chemotherapy can increase progression-free survival.[25] Perioperative chemotherapy in colorectal liver metastasis is being used with increasing frequency, although toxicity to healthy liver tissue from these agents remains a concern.[4-6] Several previous studies reported that chemotherapy is associated with the development of pathologic lesions in liver tissue.[4-6] Peppercorn, *et al.*, found that 47% of patients treated with fluorouracil developed steatosis.[26] Vauthey, *et al.*, reported that irinotecan was associated with steatohepatitis in 20.2% of their patients.[27] In a study by Rubbia-Brandt, *et al.*, 78% of patients treated with oxaliplatin developed sinusoidal dilation.[22] Viganò, *et al.*, reported nodular regenerative hyperplasia (NRH) in 21.4% of patients who underwent liver resection for colorectal liver metastasis after administration of oxaliplatin.[28]

In this study, the incidence of liver injury was higher in the CMT group than in the non-CMT group, although the difference between groups was trivial (65.9% vs. 62.5%; p=0.902).

Importantly, the pathologic findings in patients with chemotherapy-induced steatosis/steatohepatitis are

TABLE 6. Univariate and multivariate analysis of factors associated with liver injury in patients with colorectal liver metastasis.

			Univariate		Multivariate	
	No injury	Injury	Odds ratio (95% CI)	*p*-value	Adjusted odds ratio[a] (95% CI)	*p*-value
Age (mean ± SD)	58.1±11.3	60.2±10.7	1.02 (0.98-1.06)	0.373	1.02 (0.97-1.08)	0.358
Gender						
Male	15 (45.5%)	35 (59.3%)				
Female	18 (54.5%)	24 (40.7%)				
Diabetes						
Yes	4 (12.1%)	14 (23.7%)	2.26 (0.68-7.53)	0.186	1.36 (0.35-5.31)	0.654
No	29 (87.9%)	45 (76.3%)				
Hypertension						
Yes	12 (36.4%)	27 (45.8%)	1.48 (0.62-3.54)	0.383	0.88 (0.29-2.7)	0.827
No	21 (63.6%)	32 (54.2%)				
Dyslipidemia						
Yes	5 (15.2%)	15 (25.4%)				
No	28 (84.8%)	44 (74.6%)				
IHD						
Yes	3 (9.1%)	4 (6.8%)				
No	30 (90.9%)	55 (93.2%)				
HBV infection						
Yes	1 (3.0%)	3 (5.1%)				
No	32 (97.0%)	56 (94.9%)				
HCV infection						
Yes	0 (0.0%)	1 (1.7%)				
No	33 (100%)	58 (98.3%)				
Obesity						
Obese	5 (15.2%)	24 (40.7%)	3.84 (1.30-11.35)	0.015*	3.95 (1.22-12.85)	0.022*
Non-obese	28 (84.8%)	35 (59.3%)				
Preoperative chemotherapy						
Yes	15 (45.5%)	29 (49.2%)	1.16 (0.49-2.73)	0.734	1.61 (0.64-4.08)	0.314
No	18 (54.5%)	30 (50.8%)				

[a]Analysis adjusted for age, diabetes, hypertension, obesity, and chemotherapy
Data presented as mean ± standard deviation or number and percentage
*A *p*-value<0.05 indicates statistical significance
Abbreviations: CI, confidence interval; SD, standard deviation; IHD, ischemic heart disease; HBV, hepatitis B virus; HCV, hepatitis C virus

similar and often indistinguishable from the pathologic findings caused by nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) caused by metabolic syndrome.[17] Metabolic syndrome has many definitions. All of those definitions include hyperglycemia or diabetes, hypertension, and obesity in their criteria.[29, 30] Several studies have reported a link between NAFLD and obesity. Wang, *et al.*, found that the percentage of subjects with NAFLD increased commensurately with increases in BMI (up to 81.9% in BMI >28.0 kg/m^2).[31] A study by Leite, *et al.*, reported that type 2 diabetes mellitus patients with NAFLD had a higher BMI and were more often obese than those without steatosis.[32]

This study has some mentionable limitations. First and consistent with the retrospective nature of this study, some patient data may have been missing or incomplete. Second, the size of the study population was relatively small. As a result, our study may have lacked sufficient power to identify all significant associations. Third, the patients enrolled in this study were from a single center. Finally, our center is Thailand's largest tertiary referral hospital, which means that our patients usually present with complicated and intransigent conditions. As such, it is possible that our findings may not be generalizable to patients with the same condition in other settings.

Of the ten factors evaluated for association in this study, including preoperative chemotherapy, obesity was the only factor found to be significantly associated with liver injury in patients with colorectal liver metastasis. The results of this study correspond with those reported from a previous study by Bower, *et al.*[24]

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