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Preoperative Chemotherapy on Functional Liver Regeneration for Colorectal Liver Metastases Assessed With ^{99m}Tc-GSA SPECT/CT Imaging

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Objective: To investigate the functional liver regeneration after chemotherapy and liver resection for colorectal liver metastases (CRLM).

Background/Purpose: Preoperative chemotherapy followed by liver resection for CRLM has been increasing; however, its negative impact on liver regeneration remains unknown.

Methods: From January 2009 to December 2013, we enrolled 40 selected patients who underwent major hepatectomy without viral hepatitis and severe liver fibrosis. CRLM patients with preoperative chemotherapy (CT-CRLM group, $n = 12$) and patients without preoperative chemotherapy (control group, $n = 28$) were evaluated. Liver volume (LV) and functional liver volume (FLV) was assessed using Tc-99m–labeled galactosyl human serum albumin (^{99m}Tc-GSA) scintigraphy, single-photon emission computed tomography (SPECT), CT-fused images. Preoperative, future remnant liver, and post 1-month values were compared.

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Results: Median course of preoperative chemotherapy was 8 (range: 6–16). Preoperative background factors were almost identical including resection rate and functional resection rate. In the CT-CRLM group and in the control group, the percentage increases in LV were 39.3% ± 29.0% and 23.2% ± 23.5% ($P = 0.037$), and FLV were 79.4% ± 43.1% and 57.0% ± 33.4% ($P = 0.417$), respectively; absolute differences in LV were 216.2 ± 155.7 cm^3 and 148.7 ± 134.7 cm^3 ($P = 0.086$) and FLV were 19.4% ± 8.5%/m^2 and 17.4% ± 7.9%/m^2 ($P = 0.235$), respectively. We found no obvious tendency for negative influence on liver functional regeneration by the preoperative regimens for CRLM.

Conclusions: Several courses of preoperative chemotherapy may not affect functional liver regeneration for CRLM patients after major hepatectomy.

Key words: Preoperative chemotherapy – Liver resection – Colorectal liver metastases – Functional liver regeneration – Tc-99m–labeled galactosyl human serum albumin scintigraphy – Single photon emission computed tomography – CT-fused images

Liver resection is the only curative treatment for colorectal liver metastases (CRLM); however, the number of patients who receive preoperative chemotherapy has been increasing because of the high recurrence rate following hepatectomy.[1,2] Oxaliplatin (OX)-based chemotherapy for colorectal cancer can extend the indications for the resection of CRLM[3,4]; however, it may induce sinusoidal obstruction in the surrounding liver parenchyma with an increase in the risk of reduced-liver regeneration after hepatectomy.[5] In a rat model, the presence of sinusoidal obstruction definitely impaired liver regeneration.[6] Bevacizumab is a monoclonal humanized antibody to vascular endothelial growth factor (VEGF) that endows a survival benefit for patients with metastatic colorectal cancer[7] and has been increasingly used in combination with chemotherapy before liver resection. Previous studies have demonstrated that bevacizumab may prevent sinusoidal obstruction in patients treated with OX-based chemotherapy for CRLM.[8–10]

Functional liver regeneration is a useful predictor of the postoperative course.[11] Poor liver regeneration is closely associated with morbidity or mortality after liver resection. Functional liver regeneration is influenced by the degree of liver fibrosis and functional resected volume.[11–13] Moreover, other preoperative factors including age, sex, nutrition status, platelet count, and comorbidities (e.g., viral hepatitis) can affect the degree of liver regeneration.[14–18] Functional liver regeneration can be correctly assessed by Tc-^{99m}–labeled galactosyl human serum albumin (^{99m}Tc-GSA) scintigraphy, single-photon emission computed tomography (SPECT), CT-fused images.[11] Functional assessment of the future remnant liver is performed to identify the patients eligible for safe and curative hepatectomy, despite being given a marginal status based on conventional volumetric assessment.[19]

The present study aimed to clarify the influence of preoperative chemotherapy and molecular-targeted therapy on functional liver regeneration in CRLM patients after major hepatectomy.

Materials and Methods

From January 2009 to December 2013, we enrolled 40 patients who underwent major hepatectomy and functional assessment of the future remnant liver at Kumamoto University Hospital's Department of Gastroenterological Surgery. Major hepatectomy was defined as the resection of ≥3 liver segments, according to the International Hepato-Pancreato-Biliary Association.[20] Low-grade liver fibrosis was defined as F0 or F1 of pathologic fibrosis staging in the Inuyama classification.[21] Viral hepatitis was defined as positive test results for the hepatitis B surface antigen or anti-hepatitis C virus antibody. All procedures involving human participants were conducted in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The Institutional Review Board of the Graduate School of Life Sciences, Kumamoto University, approved this study (approval number: 717; December 25, 2007). Informed consent was obtained from all the participants in the study.

Volumetric and functional volumetric assessment

According to our previous reports,[11,22–24] we applied a SPECT/CT system consisting of a dual-head SPECT camera and a 16-row multisection CT scanner (Symbia T16, Siemens Healthcare, Erlangen, Germany) for scintigraphy and CT imaging, respectively. After the completion of dynamic scintigrams and static SPECT images, contrast-enhanced CT was obtained. Briefly, SPECT and CT images were fused using a dedicated workstation (Ziostation2, ZIOSOFT, Tokyo, Japan). The total liver volumes, excluding tumor and future remnant liver volumes, were determined using the contrast-enhanced CT images. Percent remnant liver volume (%LV) was expressed as a percentage of the total liver volume. From the ^{99m}Tc-GSA SPECT/CT fused images, we calculated liver uptake value (LUV) as a quantitative liver functional index[11,23] for the whole liver and future remnant liver. The percent remnant functional liver volume (%FLV) was calculated as LUV of the future remnant liver/ LUV of the whole liver $\times$ 100. The ^{99m}Tc-GSA SPECT/CT fused images were obtained within 2 weeks prior to liver resection and at 1 month later.

Hepatic resection

The type of hepatectomy was selected based on the size, number, and location of the tumor; extent of vascular invasion; %LV; %FLV; and the patients' age or general condition, as described previously.[19,25] To reduce the intraoperative blood loss, we generally used the precoagulation technique, Pringle's maneuver, or hanging maneuver.[26] Laparoscopic liver resections were accepted for the patients with CRLM and the other tumors.[27,28]

Statistical Analysis

Values were expressed as median (range) or mean $\pm$ standard deviation as required. Median and mean values were estimated using the Wilcoxon or Kruskal–Wallis test, Pearson test, and Student's *t*-test. For statistical analysis, we used a statistical software package (JMP, version 9, SAS Institute, Cary, North Carolina). A value of $P < 0.05$ was considered statistically significant.

Results

A total of 40 patients underwent major resection and were divided into 2 groups: CRLM with preoperative chemotherapy (CT-CRLM; n = 12) and a control group without preoperative chemotherapy (n = 28). All the CT-CRLM patients who underwent major hepatectomy exhibited low-grade fibrosis (F0 or F1 according to the Inuyama criteria)[21] in the background liver and no viral hepatitis. Chemotherapy-naïve CRLM patients were the best candidates as a control group; however, the number of major hepatectomies among patients who received upfront hepatectomy for CRLM was small. Therefore, as a control group, we selected 28 patients from our database who underwent major hepatectomy without preoperative chemotherapy and did not have severe fibrosis and viral hepatitis. The pathologic diagnoses were CRLM (n = 15); hepatocellular carcinoma (n = 9); intrahepatic cholangiocarcinoma (n = 7); bile duct carcinoma (n = 4); and other tumors (n = 5). Patient characteristics are summarized in Table 1. All the background factors were identical, with the exception of total bilirubin levels and platelet counts; however, the median values were within the normal range for both the groups.

Serial changes in liver volume and functional liver volume

Serial changes in the volume and functional volume of the preoperative total liver, future remnant liver, and post 1-month liver measurements are displayed in Figs. 1a and 1b, respectively. After 1 month, %LV was similar ($P = 0.966$) in the CT-CRLM and control groups (74.7% $\pm$ 13.4% and 74.5% $\pm$ 11.2%, respectively). Similarly, %FLV after 1 month was similar ($P = 0.565$) in the CT-CRLM and control groups (98.1% $\pm$ 10.7% and 98.7% $\pm$ 10.7%, respectively). Furthermore, after 1 month, %FLV was significantly larger than %LV in the CT-CRLM and control groups (both $P < 0.001$).

Regeneration in liver volume and functional liver volume

In the CT-CRLM and control groups, the percentage increases in LV were 39.3% $\pm$ 29.0% and 23.2% $\pm$ 23.5%, and FLV were 79.4% $\pm$ 43.1% and 57.0% $\pm$ 33.4%, respectively (Figs. 2a and 2b). The percentage increase in LV was significantly higher in the CT-CRLM group than in the control group ($P = 0.037$), but the percentage increase in FLV was similar in the 2 groups ($P = 0.417$). The absolute differences in LV were 216.2 $\pm$ 155.7 cm^3 and 148.7 $\pm$ 134.7 cm^3 and FLV were 19.4 $\pm$ 8.5 $\%/m^2$ and 17.4 $\pm$ 7.9%/m^2, respectively (Figs. 3a and 3b). The absolute differ-

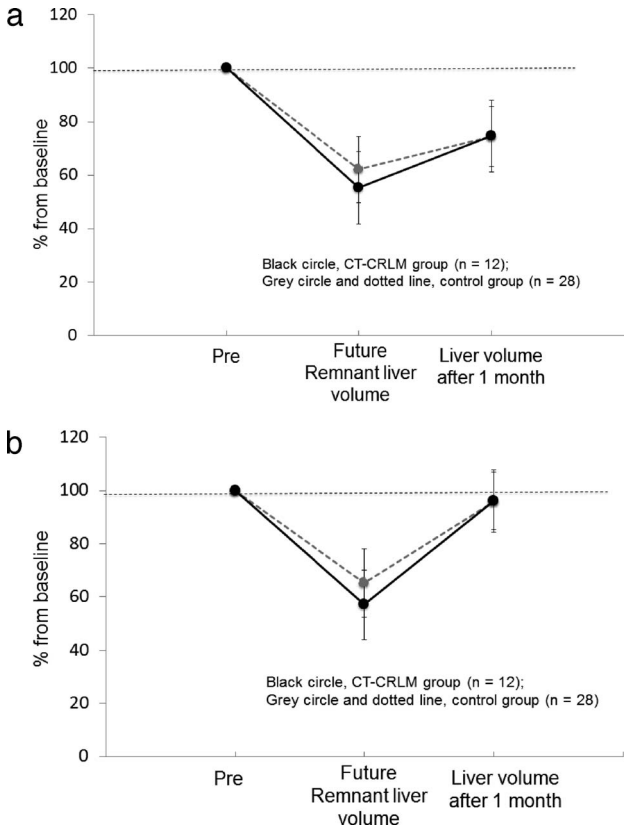

Fig. 1 Serial changes in liver volume and functional liver volume. (a) Liver volume. (b) Functional liver volume. Black circle, CT-CRLM group (n = 12); grey circle and dotted line, control group (n = 28).

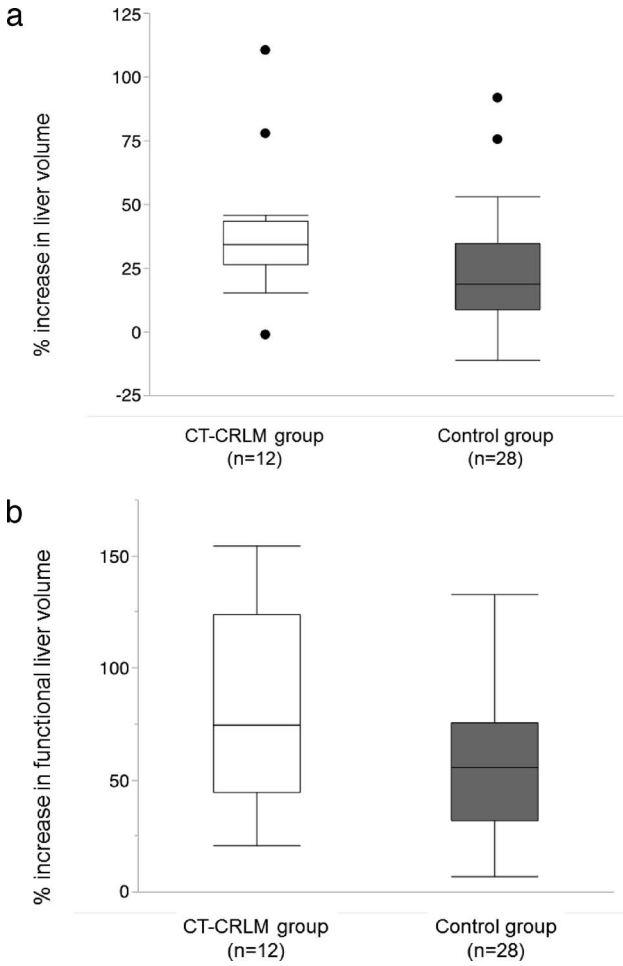

Fig. 2 Percentage increases in liver volume and functional liver volume before and after liver resection. (a) Liver volume. (b) Functional liver volume. Bar in the box and whisker plots: 1.5 interquartile ranges of the upper quartile, 75% percentile, median, 25% percentile, and 1.5 interquartile ranges of the lower quartile.

ences in LV and FLV were equivalent between the 2 groups ($P = 0.086$ and 0.235, respectively).

Postoperative liver function

Median postoperative total bilirubin levels (0.6 mg/dL versus 0.7 mg/dL); prothrombin activities (93% versus 93%); the uptake ratio of the heart at 15 minutes compared to 3 minutes (0.58 versus 0.53); and the uptake ratio of the liver compared to the liver plus the heart at 15 minutes (0.92 versus 0.94) determined through ^{99m}Tc-GSA scintigraphy were equivalent between the CT-CRLM and control groups.

Regeneration of liver volume and functional liver volume in CRLM patients

The data of 15 CRLM patients are described in Table 2. The median age was 64.7 ± 11.6 years, and the female-to-male ratio was 6:9. In 12 CRLM patients with preoperative chemotherapy and 3 chemotherapy-naïve CRLM patients, the mean resection rate/functional resection rate was 44.3% ± 12.3%/42.3% ± 11.5% and 42.7% ± 11.1%/39.9% ± 7.3%, and the mean percentage increase in LV/FLV from the baseline values of the future remnant liver was 36.6% ± 27.7%/73.4% ± 37.7% and 24.5% ± 29.0%/145.4% ± 55.1%, respectively. There were no significant differences between CRLM patients with and without chemotherapy. Among the 12 CRLM patients with preoperative chemotherapy, OX; irinotecan (IRI); and OX + IRI were administered to 8, 1, and 3 patients, respectively. Bevacizumab was initiated in 3 patients, antiepidermal growth factor

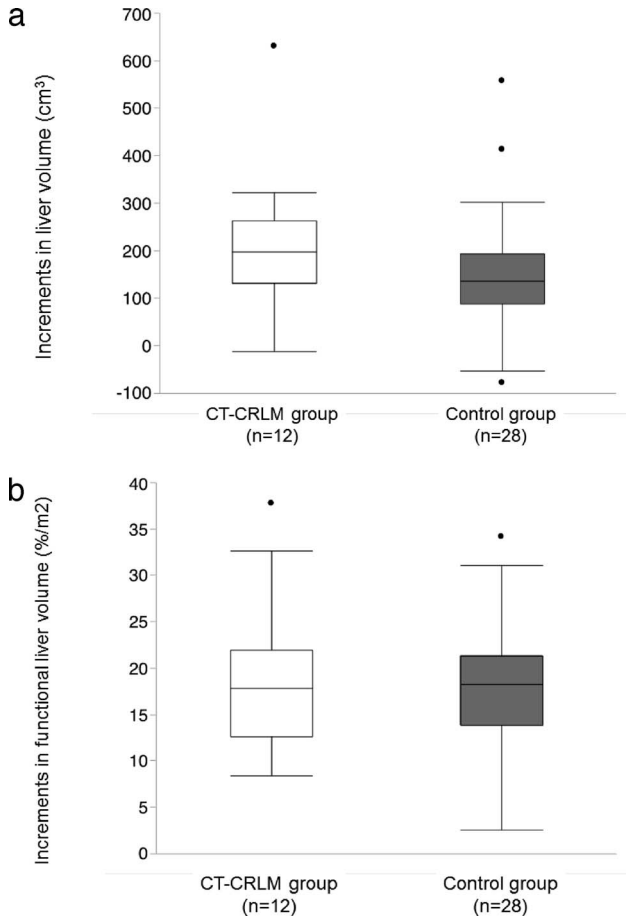

Fig. 3 Increments in liver volume and functional liver volume before and after liver resection. (a) Liver volume. (b) Functional liver volume. Bar in the box and whisker plots: 1.5 interquartile range of the upper quartile, 75% percentile, median, 25% percentile, and 1.5 interquartile range of the lower quartile.

receptor antibody in 2 patients, and both treatments were administered to 3 patients. The median number of preoperative chemotherapy courses was 8 (range: 6–16). The number in treatment of 3-week regimens was counted as 1.5 times of 2-week regimens. Various types of major hepatectomies were performed. We observed no distinct differences in LV and FLV with regard to the regimens and cycles of preoperative therapy. We assessed 6 out of 15 (40%) patients as having grade 2 or greater sinusoidal obstruction[9]; all the patients received OX-containing chemotherapy, and 4 patients were treated without bevacizumab. No patients exhibited steatohepatitis with nonalcoholic fatty liver disease activity score >4.[29]

Discussion

Recently, we have reported that the functional liver regeneration, and not the volumetric liver regeneration, as assessed by ^{99m}Tc-GSA SPECT/CT fused images, can correctly predict the levels of postoperative liver dysfunction.[11] The functional liver regeneration was influenced by the degree of liver fibrosis and the functional resected volume, and the existence of viral hepatitis.[12–14,16] Therefore, as a control group, we selected patients who underwent major hepatectomy without preoperative chemotherapy and who did not have severe fibrosis and viral hepatitis. The preoperative background factors, including liver function, functional resection rate, and future remnant FLV, were almost equivalent. Total bilirubin levels and platelet counts significantly differed between the 2 groups; however, the median values were within the normal range. Because platelet-derived serotonin is associated with the initiation of liver regeneration, decrease in platelet counts may negatively impact liver regeneration.[17] In the present study, both liver regeneration and functional liver regeneration parameters were equivalent between the CT-CRLM and control groups. Conversely, percentage increases in LV were somewhat greater in the CT-CRLM group.

Modern chemotherapy for CRLM can induce various liver parenchymal injuries such as steatosis, steatohepatitis, and sinusoidal obstruction. Liver regeneration within 1 week after hepatectomy did not differ between patients with and without steatosis.[30] However, when only patients with moderate-to-severe steatosis (steatosis $\geq$30%) were considered, the late liver regeneration after 6 months in the steatosis patients was lower. In a mouse model, steatosis did not impair liver regeneration after partial hepatectomy.[31] Moreover, simple steatosis prompted by Western diet–induced steatosis can enhance liver cell proliferation, which was accompanied by increased hepatocyte growth factor and leptin signaling. In contrast, in rats fed on a standard methionine- and choline-deficient diet, steatohepatitis probably impaired liver regeneration because of increased hepatocellular lipid peroxidation and damage in concert with Kupffer cell–mediated inflammatory responses.[32] In the present study, no patients exhibited moderate-to-severe steatosis (steatosis $\geq$30%) or apparent steatohepatitis.

VEGF is one of the key molecules for liver regeneration, and bevacizumab is an anti-VEGF

Table 1 Preoperative clinical characteristic

	CT-CRLM group (n = 12)	Control group (n = 28)	*P* value
Age	64 (36–80)	63 (37–81)	0.64
Sex, M:F	7:5	19:9	0.72
Diagnosis, n	CRLM, 12	CRLM, 3; HCC, 9; ICC, 7; BDC, 4; other tumors, 5	NE
ICG R15 (%)	12.6 (5.6–26.3)	7.9 (2.8–73)	0.071
HH15	0.58 (0.39–0.73)	0.525 (0.42–0.71)	0.13
LHL15	0.93 (0.85–0.97)	0.95 (0.87–0.97)	0.22
Total bilirubin	0.55 (0.3–1.1)	0.8 (0.4–4.3)	0.006
Albumin	3.8 (3–4.3)	4.3 (2.6–5.1)	0.058
AST	33.5 (19–137)	29 (15–217)	0.51
ALT	31.5 (10–281)	28.5 (11–285)	0.91
Total cholesterol	191 (154–256)	182 (142–297)	0.85
Choline esterase	254 (155–312)	265.5 (178–537)	0.44
Prothrombin time activity (%)	107 (96–150)	98 (85–143)	0.64
Platelets count	16.9 (9.4–23.8)	19.75 (12.9–44.8)	0.049
Fibrosis-stage, F0:F1	4:8	12:16	0.73
PVE, yes:no	3:9	5:23	0.61
Total liver volume, cm^3 (range)	1144.5 (782–1435)	1249.5 (720–1652)	0.21
Resection rate, % (range)	42.6 (21.5–65.0)	35.2 (12.1–61.3)	0.13
Future remnant liver volume, cm^3 (range)	563 (414–984)	702.5 (384–1245)	0.06
Preoperative total LUV, $\%/m^2$ (range)	46 (35–64.4)	51.3 (40.0–69.8)	0.16
Functional resection rate, % (range)	45.0 (18.0–62.0)	33.8 (11.7–60.0)	0.072
LUV of the future liver, $\%/m^2$ (range)	24.8 (16.4–41)	33.15 (18.3–47.6)	0.042

ALT, alanine aminotransferases; AST, aspartate aminotransferases; BDC, bile duct carcinoma; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; ICG R15, 15-minute indocyanine retention rate; HH15, uptake ratio of the heart at 15 minutes compared to 3 minutes; LHL15, uptake ratio of the liver to the liver plus heart at 15 min; LUV, liver uptake value; NE, not evaluated; PVE, portal vein embolization.

monoclonal antibody. In the present study, 6 patients received bevacizumab-containing chemotherapy; however, no obvious liver regeneration failure was noted. Meanwhile, OX-based chemotherapy can induce sinusoidal obstruction, with the risk of impairing postoperative liver regeneration,[5,6] and this adverse effect may be avoided by using bevacizumab but not cetuximab or panitumumab.[8,9] A case-matched study recently demonstrated that bevacizumab did not impair liver regeneration after

Table 2 Regeneration data in CRLM patients

Pts' no.	Sex	Age	Chemo regimen	Target drug	Chemo cycle	OP method	Total liver volume, cm^3	Future remnant liver volume, cm^3	Liver volume 1 mo, cm^3
1	M	73	OX	None	8	Rt-hemi + Lateral	966	586	788
2	M	57	OX	None	9	Rt-hemi	1365	571	1202
3	M	80	OX	None	7	Lt-hemi	782	452	579
4	M	78	OX	None	10	Lateral + S7 + S8	1254	984	973
5	M	75	OX	B	6	Lt-hemi	1103	800	922
6	M	69	OX	B	7	Post + Ant-dor	1356	774	1042
7	F	64	OX	C	8	Rt-hemi	1065	486	630
8	M	63	OX	P	8	Lt-3 section	1199	604	810
9	F	60	OX, IRI	B + P	16	Rt-hemi + S2	1186	414	736
10	F	64	OX, IRI	B + C	16	Post + S2	807	540	788
11	F	36	OX, IRI	B + P	7	Rt-hemi	1435	555	700
12	F	51	IRI	B	10	Rt-hemi	902	529	720
13	M	79	None	None	0	Rt-hemi	1114	496	758
14	M	66	None	None	0	Lt-hemi + S1	1361	877	1102
15	F	55	None	None	0	Lt-hemi	1652	1042	989

Ant-dor, anterior dorsal hepatectomy; B, bevacizumab; C, cetuximab; chemo, chemotherapy; hemi, hemihepatectomy; lateral, lateral sectionectomy; LUV, liver uptake value; OP, operation; P, panitumumab; post, posterior sectionectomy.

major hepatectomy even in patients with high exposure to preoperative chemotherapy.[33] In a clinical report, liver regeneration was not adversely affected by chemotherapy, including molecular-targeted drugs for patients with a high grade of steatosis or sinusoidal obstruction in the surrounding liver parenchyma.[34] Portal vein embolization (PVE) can provide liver regeneration similar to that by major hepatectomy.[22] One report described that chemotherapy with bevacizumab did not affect liver regeneration after PVE.[35] In contrast, bevacizumab may impair liver regeneration after PVE, and an age >60 years and treatment with ≥6 cycles of bevacizumab were risk factors for poor regeneration.[36] In the present study, 6 out of 15 (40%) patients were assessed as having grade 2 or higher sinusoidal obstruction; all patients received OX and 4 were treated without bevacizumab. In all 15 CRLM patients, FLV increased, with a mean increment of 73.4% ± 37.7%; conversely, LV decreased in 2 patients, and the mean increment was 36.6% ± 27.7%. The percent increases in LV and FLV were not always correlated patient-by-patient (data not shown). There were no obvious differences in both volumetric and functional liver regeneration with regard to the differences in chemotherapeutic regimens.

To our knowledge, the present report is the first to elucidate that both functional liver regeneration and volumetric liver regeneration after major hepatic resection are unaffected by preoperative chemotherapy for CT-CRLM patients; however, our study has some limitations. First, for CRLM, limited hepatectomy has been more frequently selected instead of major hepatectomy, and preoperative chemotherapy has often been employed[1,2]; therefore, the number of patients undergoing major hepatectomy, particularly without preoperative chemotherapy, was small. In this paper, the results of the CT-CRLM patients were mainly compared with those of patients with various liver tumors. However, there were no significant differences in liver regeneration data between CRLM patients with and those without chemotherapy. Second, various chemotherapies were administered in a neoadjuvant or conversion manner[2–4]; therefore, the number or duration of chemotherapy was not constant. Third, our study did not include cases of extremely extensive resection or resection in extremely damaged livers. Finally, the assessment of functional liver regeneration with ^{99m}Tc-GSA SPECT/CT fused images has not been applied outside Japan.

Conclusion

Preoperative chemotherapy may not affect functional liver regeneration in patients who receive several courses of OX- or IRI-based chemotherapy with molecular-targeted drugs. Further prospective and large-scale studies are required to confirm these results, using the same regimen and treatment duration in CRLM patients with or without preoperative chemotherapy.

Table 2 Extended

Resection rate, %	Volume gain, %	Preoperative total LUV, %/m^2	LUV of the future liver, %/m^2	LUV 1 mo, %/m^2	Functional resection rate, %	LUV gain, %
39.3	38.0	40.0	24.4	44.8	39.1	186.3
58.1	110.4	45.0	22.1	33.8	50.9	47.5
42.2	28.1	47.0	28.3	48.6	39.8	159.8
21.5	–1.1	50.0	41	48.1	18.0	433.6
27.5	15.3	45.0	34.3	44.7	23.9	316.0
42.9	34.6	38.0	18.2	36.9	52.0	86.8
54.4	29.7	43.0	21.5	35.9	50.1	66.7
49.6	34.1	35.0	16.4	37.4	53.2	100.9
65.1	77.8	64.4	24.5	62.3	62.0	56.1
33.1	45.9	61.0	39	54.5	36.1	147.6
61.3	26.1	53.3	25	56.1	53.2	97.8
41.4	36.2	53.0	33.5	49.5	36.7	154.3
55.5	52.9	45.0	23.5	41.2	47.8	91.6
35.6	25.7	45.0	30	45.3	33.4	201.7
36.9	–5.1	54.0	33.1	50.7	38.6	142.8

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