Chemotherapy and Its Effect on Liver Hypertrophy: Implications for Portal Vein Embolization and Resection

Antoine Brouquet, M.D.,[1] and Jacques Belghiti, M.D.[1]

ABSTRACT

Liver resection remains the gold standard treatment for colorectal liver metastases (CRLM). The improvement of the efficacy of chemotherapy has resulted in an increase of CRLM candidates for curative resection, including a significant proposition of patients initially deemed unresectable. The safety of liver resection has increased by taking advantage of regenerative capacities of the liver with preoperative portal vein embolization (PVE) and two-stage strategies. However, chemotherapy regimens including new drugs such as oxaliplatin and irinotecan may induce pathologic changes of the nontumorous liver parenchyma that could increase the risk of liver resection, and the impact of chemotherapy on the nontumorous liver parenchyma may limit tolerance of these resections. Preoperative portal obstruction, including PVE, which aimed to hypertrophy the future remnant liver, can be adversely affected by this chemotherapy. The aim of this article is to describe the impact of chemotherapy on nontumorous liver parenchyma and to evaluate the impact of chemotherapy on the regenerative capacities of the liver, especially after PVE.

KEYWORDS: Colorectal liver metastases, chemotherapy, hepatotoxicity, portal vein obstruction

Objectives: Upon completion of this article, the reader should be able to determine the impact of chemotherapy for colorectal liver metastases on liver regeneration.
Accreditation: Tufts University School of Medicine (TUSM) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.
Credit: TUSM designates this educational activity for a maximum of 1 *AMA PRA Category 1 Credit*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Liver resection remains the gold standard treatment of resectable colorectal liver metastases (CRLM).[1] In patients with unresectable liver metastases, chemotherapy, which was initially used with a palliative intent, has considerably improved the response rate of CRLM during the last decade. Tumor responses increased from 15 to 20% with fluorouracil (5-FU) and to 40 to 50% with oxaliplatin and irinotecan.[2,3] A tumor response $>60\%$ can be obtained by combining targeted therapies, including bevacizumab and cetuximab, with a conventional chemotherapy regimen.[4,5] This improvement of the efficacy of chemotherapy has resulted in an increase

[1]HPB Surgery Department, Hospital Beaujon, Paris, France.
Address for correspondence and reprint requests: Jacques Belghiti, M.D., HPB Surgery Department, Hospital Beaujon, 100 Boulevard du Général Leclerc, 92110 Clichy, France (e-mail: jacques.belghiti@bjn.aphp.fr).

Portal Vein Embolization; Guest Editors, David C. Madoff, M.D., and Thierry de Baere, M.D.
Semin Intervent Radiol 2008;25:162–167.
DOI 10.1055/s-2008-1076682. ISSN 0739-9529.

of CRLM candidates for a curative resection. Therefore, in addition to the 10 to 15% of patients with initially unresectable disease who become resectable after chemotherapy,[6,7] there is a trend to use preoperative chemotherapy in all resectable patients because perioperative chemotherapy improves overall survival.[8]

At the same time, the safety of extensive liver resection has increased by taking advantage of the regenerative capacity of the liver with preoperative right portal vein embolization (PVE) and the two-stage strategy.[9–13] However, the impact of chemotherapy on the nontumorous liver parenchyma may limit tolerance of these resections.[14] Chemotherapy, especially oxaliplatin and irinotecan, may induce histopathological changes of the nontumorous liver parenchyma that could adversely affect regenerative capacities of the liver.[15,16] An increased risk of postoperative liver failure after major hepatectomy has been reported.[17,18] Preoperative portal obstruction, including PVE and portal vein ligation (PVL), can reduce this risk.[9,10,12] Chemotherapy is usually discontinued 1 month prior to liver resection because it is alleged to impair liver hypertrophy of the future remnant liver (FRL).[19] The risk of tumor progression during the 2-month interval between the last cycle of chemotherapy and liver resection led us to discontinue chemotherapy during this preparation.[20] This article evaluates the impact of chemotherapy on the regenerative capacities of the liver, especially after PVE.

PREOPERATIVE CHEMOTHERAPY AND THE RISK OF LIVER RESECTION

The vast majority of patients referred for CRLM are treated by chemotherapy with an increasing rate of efficiency. However, the impact of these new drugs can alter liver parenchyma, liver function, and consequently surgical outcome following liver resection, and thus they are an issue of debate. Numerous studies have evaluated morbidity and mortality following liver resection for colorectal metastases after neoadjuvant chemotherapy with discordant results (Table 1).[17,18,21–26]

Several factors can explain this discrepancy of results, including modalities of chemotherapy (type of main drug used, duration of chemotherapy, and the interval between chemotherapy and liver resection) and the extent of resection. The two series[17,18] showing an adverse impact of preoperative chemotherapy were characterized by a relatively short interval between the last cycle and liver resection, a chemotherapy regimen based on irinotecan or oxaliplatin, and a major liver resection in the majority of patients.

The evaluation of perioperative use of targeted therapies on postoperative outcome following liver resection was conducted in one study including 32 patients.[27] In this study, 8 patients received preoperative bevacizumab-based chemotherapy, 16 patients received

Table 1 Impact of Preoperative Chemotherapy for Colorectal Liver Metastases on Surgical Outcome Following Liver Resection

Series	Number of Patients	FU-Based Chemotherapy	Oxaliplatin-Based Chemotherapy	Irinotecan-Based chemotherapy	Mean Number of Cycles	Interval between Chemotherapy and Liver Resection (wk)	Major (≥ 3 Liver Segments) /Minor Liver Resection	Impact of Chemotherapy on Postoperative Morbidity	Impact of Chemotherapy on Postoperative Mortality
Parc et al[21]	17	17 (100%)	0	0	NA	< 12	17	No	No
Yedibela et al[22]	32	NA	NA	NA	NA	NA	9–23	No	No
Karoui et al[17]	45*	12 (25%)	38 (84.4%)	14 (31.1%)	6	< 8	45	Yes	No
Vauthey et al[18]	248	63 (25.4%)	79 (31.8%)	94 (37.9%)	8 (16 wk)	6.4	163/85	No	Yes†
Aloia et al[23]	75	52 (69%)	23 (31%)	0	> 6 for 46 patients	< 24	43/32	No	No
Sahajpal et al[24]	53	35 (66%)	9 (17%)	0	5.7	12	43; ≥ 2 liver segments	No	No
Hewes et al[25]	46	25 (54%)	21 (46%)	1 (2%)	6	< 60	NA	No	No
Pawlik et al[26]	153	67 (44%)	55 (36%)	31 (20.2%)	< 6 for 99 patients	NA	64/89	No	No

*Some patients received more than one line of chemotherapy regimen.
†Irinotecan-based chemotherapy was associated with chemotherapy-associated steatohepatitis (CASH); CASH was associated with increased 90 days postoperative mortality.
FU, fluorouracil; NA, not applicable.

Table 2 Correlation between Postoperative Outcome Following Liver Resection and Liver Parenchyma Changes Associated with Preoperative Use of Chemotherapy

Liver Parenchyma Changes	Morbidity Following Liver Resection	Mortality Following Liver Resection	Authors
Steatosis	+	0	Kooby et al[28]
			Belghiti et al[29]
			Gomez et al[30]
CASH	+++	+	Vauthey et al[18]
SOS	++	0	Karoui et al[17]
			Aloia et al[23]

CASH, chemotherapy-associated steatohepatitis; SOS, sinusoidal obstruction syndrome.

postoperative bevacizumab-based chemotherapy, and 8 patients received both pre- and postoperative bevacizumab. The median number of doses of bevacizumab provided was 9 (range, 4 to 15) preoperatively and 8 (range, 1 to 16) postoperatively. The median interval between the last cycle of preoperative bevacizumab and the liver resection was 6.9 weeks (range, 3 to 15) and between surgery and the first cycle of postoperative bevacizumab was 7.4 weeks (range, 5 to 15). Of the 32 patients, 17 underwent a major liver resection. Postoperative outcomes of these patients were compared with those of 32 matched patients who were not treated with bevacizumab. Overall, postoperative complications (two considered major) occurred in 13 patients (40.7%). Although the impact of bevacizumab on regeneration after major hepatectomy has not been studied, according to this research, there is no argument demonstrating an increased risk of liver resection for CRLM in patients treated by targeted therapies.

CHEMOTHERAPY-ASSOCIATED HEPATOTOXICITY

Chemotherapy for CRLM is associated with different patterns of histopathological changes of the non-tumor-bearing liver (Table 2).[17,18,23,28–30] Steatosis was observed in 30 to 47% of patients receiving systemic FU-based chemotherapy.[31–33] Although no convincing argument shows an increased risk of liver resection due to chemotherapy-induced hepatic steatosis, severe steatosis due to diabetes mellitus and obesity is associated with increased morbidity rates.[28–30] Therefore, patients with severe steatosis who are candidates for CRLM resection have an increased risk of complications and blood transfusion, whatever the pathogenesis of steatosis.[30]

More recently, two major histopathological entities related to the use of chemotherapy were defined: chemotherapy-associated steatohepatitis (CASH)[16] and sinusoidal obstruction syndrome (SOS).[15] An increasing number of studies suggest that the use of a chemotherapy regimen including oxaliplatin and irinotecan may be responsible for the occurrence of these lesions. However, the natural history of CASH and SOS and their impact on liver function are still unknown. Vauthey et al[18] observed that CASH occurred in 8.4% of patients treated by neoadjuvant chemotherapy with an increased risk in patients with a body mass index >25 kg/m^2 treated by irinotecan. In this study, CASH was associated with an increased mortality rate following liver resection (14.7% versus 1.6%; $p=0.001$). SOS was initially described in the setting of bone marrow transplantation where its occurrence was associated with a high mortality rate.[34,35] Rubbia-Brandt et al[15] reported that oxaliplatin-based chemotherapy may induce SOS lesions in 78% of patients treated for CRLM. The impact of SOS on postoperative outcomes has been studied in several reports. Aloia et al[23] showed that severe vascular lesions were associated with increased intraoperative transfusions, but no major consequences on morbidity and mortality were observed. Karoui et al[17] demonstrated in a series of patients who mainly received oxaliplatin (40 of 67) that this chemotherapy was associated with an increased morbidity due to postoperative liver dysfunction. Chemotherapy was associated with microvascular changes and hepatocyte necrosis, but liver injuries were not stratified according to the chemotherapy regimen.

However, according to the literature, no clear argument shows that patients with CASH and/or SOS are impaired regarding the regenerative capacities of the liver or an increase in postoperative dysfunction.

LIVER HYPERTROPHY FOLLOWING PVE OR PVL

Mechanisms of liver hypertrophy are complex and associated with multiple factors, but it is well demonstrated that the portal flow has a hepatotrophic effect.[36] Unilateral portal vein occlusion induces an atrophy of the ipsilateral liver lobe and a hypertrophy of the remnant liver. Makuuchi et al[37] reported that fatal liver failure did not occur after major liver resection when the portal vein of the resected lobe was obstructed. This group capitalized on this finding to advocate preoperative PVE to initiate compensatory hypertrophy of the FRL. Azoulay et al[38] reported their experience of 30 patients with colorectal hepatic metastases initially considered unresectable because of inadequate liver remnant that became resectable after chrono-modulated chemotherapy followed by PVE. PVE induced a median 42% liver volume gain in liver remnant volume and allowed resection in 19 of 30 patients (63%). There was no instance of postoperative liver failure, and the actuarial 5-year survival for the resected patients was 40%. Several other authors have confirmed the applicability of this approach to increase the resectability rate for colorectal liver

metastases. The FRL volume limit for safe resection varies from patient to patient. Guidelines have evolved from analysis of outcomes after extended hepatectomy.[39] In patients with an otherwise normal liver, PVE is indicated when the standardized FRL volume is $\leq 20\%$. This cutoff point was determined by the analysis of complications in 42 patients with a normal underlying liver who underwent extended right hepatectomy.[13] The complication rate was increased, and intensive care unit stay and hospital stay were prolonged in patients with an FRL volume $\leq 20\%$ compared with those with an FRL volume $> 20\%$. No patient died in the series. Among patients who receive extensive chemotherapy prior to hepatic resection, liver injury can occur.[14] Although the clinical significance of chemotherapy-related liver injury is not well defined, it has been proposed to prepare for a major hepatectomy with preoperative PVE in patients who have received preoperative systemic chemotherapy with the stigmata of CASH and/or SOS.[14,40,41]

Our group[10] reported an all-surgical two-stage approach for patients presenting with synchronous hepatic metastases where PVL was performed at the time of the initial exploration for bowel resection, sometimes associated with resection of left-side CRLM, to induce hypertrophy of the FRL. We, and others,[42,43] recently showed that right PVL and PVE result in a comparable hypertrophy of the left liver and that PVL can be performed efficiently and safely during the first laparotomy of a two-step liver resection.

Hence improved understanding of the benefits of liver regeneration has allowed portal vein occlusion to increase the pool of patients who can safely undergo potentially curative hepatic resection.

HEPATIC REGENERATION AND CHEMOTHERAPY

Liver Regeneration and Neoadjuvant Chemotherapy

Gruenberger et al[44] have evaluated the impact of preoperative chemotherapy on surgical outcome following hepatic resection. In this study, liver regeneration was assessed by a computed tomography scan performed 3 months after liver resection. Fifty-four patients received six cycles of preoperative oxaliplatin-based chemotherapy (XELOX) with bevacizumab. The sixth cycle of chemotherapy did not include bevacizumab, resulting in a 5-week interval between the last bevacizumab dose and the liver resection. Forty-eight patients underwent a curative liver resection after completing chemotherapy. Among these 48 patients, 17 underwent a major liver resection (three or more liver segments) and 9 patients had a combined resection of the primary tumor. There were no postoperative deaths, and morbidity was encountered in 8 (17%) patients. In this study, preoperative chemotherapy including bevacizumab had no worse effect on postoperative course following hepatic resection. Liver regeneration assessed at 3 months was reported to be normal in all but one patient (related to steatohepatitis).

Numerous studies have evaluated the impact of preoperative chemotherapy on postoperative outcome following hepatectomy (Table 1), but liver regeneration was not assessed in these studies.

Liver Regeneration and Postoperative Chemotherapy

Little data are available on liver regeneration and postoperative chemotherapy in humans. Adjuvant chemotherapy following a hepatic resection is mostly reintroduced when the patient is discharged, that is, 4 to 6 weeks after the operation. However, there are several studies on liver regeneration following hepatectomy in rats treated postoperatively by chemotherapy. Engum et al[45] evaluated liver regeneration in five groups of rats after 70% hepatectomy. Group I (untreated controls, $n = 32$) received 0.9% saline intraperitoneally (IP); group II ($n = 31$): cisplatin, 4 mg/kg IP; group III ($n = 36$): cisplatin, 10 mg/kg IP; group IV ($n = 34$): cisplatin, 20 mg/kg IP; and group V ($n = 27$): doxorubicin, 6 mg/kg intravenously. Liver regeneration was evaluated by liver weight, DNA incorporation measured by titrated thymidine (^{3}H-TdR), and quantitative image analysis (QIA) of hepatic nuclei at 18, 24, 36, 48, and 72 hours, and 5 days postoperatively. The study showed that (^{3}H-TdR) DNA incorporation was not inhibited by cisplatin. QIA, however, showed a dose-dependent inhibition with 4 mg/kg, 10 mg/kg, and 20 mg/kg cisplatin administration. The authors concluded that early use of cisplatin (4 mg/kg is two times the human dose) following hepatic resection is feasible and may reduce the risk of local recurrence and/or metastatic spread.

Liver Hypertrophy following PVE and Chemotherapy

Histopathological changes of the nontumorous liver parenchyma associated with chemotherapy could adversely affect the regenerative capacities of the liver and consequently increase the risk of major liver resection. For this reason, some authors have proposed performing PVE or PVL in this context. This strategy has two major advantages: First, PVE leads to a hypertrophy of the FRL and prevents the risk of postoperative liver dysfunction; second, PVE allows a preoperative assessment of the regenerative capacities of the liver. A theoretical drawback of this strategy is that chemotherapy is usually discontinued in the interval between PVE and liver resection because it has been alleged to impair liver hypertrophy, leading to an increased risk of

tumor progression during this period. Two studies have evaluated the hypertrophy of the liver following PVE in patients treated by chemotherapy for colorectal liver metastases. Goere et al[20] compared 10 patients treated by chemotherapy in the interval between PVE and hepatectomy and 10 without chemotherapy. In the chemotherapy group, patients received mainly a FU-based chemotherapy associated with either oxaliplatin or irinotecan. In this study, chemotherapy had no adverse effects on liver hypertrophy following PVE ($33 \pm 26\%$ in the chemotherapy group versus $25 \pm 7\%$). On the contrary, in the study of Beal et al,[19] chemotherapy administrated in the interval between PVE (mainly oxaliplatin-based chemotherapy, 60%) and hepatectomy impaired liver hypertrophy (89 mL; range, 7 to 149 mL in the chemotherapy group [$n = 10$] versus 135 mL, 110 to 254 mL in patients without chemotherapy [$n = 5$]; $p = 0.016$). In this latter study, patients without chemotherapy were more likely to have tumor progression between the PVE and the hepatectomy. The authors concluded that peri-procedure chemotherapy did not prevent but did reduce liver hypertrophy following PVE. In addition, a trend toward tumor progression in patients not treated with peri-procedure chemotherapy was observed.

In conclusion, some arguments suggest an adverse effect on the regenerative capacities of the liver after the use of new cytotoxic agents such as irinotecan and cisplatin and targeted therapies for CRLM. The impact of histopathological changes induced by these agents remains unclear. Therefore it seems logical to propose preoperative PVE or PVL in patients in whom a major hepatectomy is considered. Although no recommendations for the peri-procedure use of chemotherapy can be proposed on the basis of the data in the literature, the risk of tumor progression when the chemotherapy is discontinued necessitates it be taken into account.

REFERENCES

1. Scheele J, Stang R, Altendorf-Hofmann A, et al. Resection of colorectal liver metastases. World J Surg 1995;19:59–71
2. Douillard JY, Cunningham D, Roth AD, et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. Lancet 2000;355:1041–1047
3. De Gramont A, Figer A, Seymour M, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol 2000;18:2938–2947
4. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004;350:2335–2342
5. Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med 2004; 351:337–345
6. 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;240:644–657
7. Leonard GD, Brenner B, Kemeny NE. Neoadjuvant chemotherapy before liver resection for patients with unresectable liver metastases from colorectal carcinoma. J Clin Oncol 2005; 23:2038–2048
8. Nordlinger B, Sorbye H, Collette B, et al. Final results of the EORTC Intergroup randomized phase III study 40983 [EPOC] evaluating the benefit of peri-operative FOLFOX4 chemotherapy for patients with potentially resectable colorectal cancer liver metastases. 2007 ASCO Annual Meeting Proceedings Part I. Journal of Clinical Oncology 2007;25(18 suppl)
9. Jaeck D, Oussoultzoglou E, Rosso E, et al. A two-stage hepatectomy procedure combined with portal vein embolization to achieve curative resection for initially unresectable multiple and bilobar colorectal liver metastases. Ann Surg 2004;240:1037–1049
10. Kianmanesh R, Farges O, Abdalla EK, et al. Right portal vein ligation: a new planned two-step all-surgical approach for complete resection of primary gastrointestinal tumors with multiple bilateral liver metastases. J Am Coll Surg 2003; 197:164–170
11. Farges O, Belghiti J, Kianmanesh R, et al. Portal vein embolization before right hepatectomy: prospective clinical trial. Ann Surg 2003;237:208–217
12. Adam R, Laurent A, Azoulay D, et al. Two-stage hepatectomy: a planned strategy to treat irresectable liver tumors. Ann Surg 2000;232:777–785
13. Abdalla EK, Barnett CC, Doherty D, et al. Extended hepatectomy in patients with hepatobiliary malignancies with and without preoperative portal vein embolization. Arch Surg 2002;137:675–680
14. Zorzi D, Laurent A, Pawlik TM, et al. Chemotherapy-associated hepatotoxicity and surgery for colorectal liver metastases. Br J Surg 2007;94:274–286
15. Rubbia-Brandt L, Audard V, Sartoretti P, et al. Severe hepatic sinusoidal obstruction associated with oxaliplatin-based chemotherapy in patients with metastatic colorectal cancer. Ann Oncol 2004;15:460–466
16. Fernandez FG, Ritter J, Goodwin JW, et al. Effect of steatohepatitis associated with irinotecan or oxaliplatin pretreatment on resectability of hepatic colorectal metastases. J Am Coll Surg 2005;200:845–853
17. Karoui M, Penna C, Amin-Hashem M, et al. Influence of preoperative chemotherapy on the risk of major hepatectomy for colorectal liver metastases. Ann Surg 2006;243:1–7
18. Vauthey JN, Pawlik TM, Ribero D, et al. Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. J Clin Oncol 2006;24:2065–2072
19. Beal IK, Anthony S, Papadopoulou A, et al. Portal vein embolisation prior to hepatic resection for colorectal liver metastases and the effects of periprocedure chemotherapy. Br J Radiol 2006;79:473–478
20. Goere D, Farges O, Leporrier J, et al. Chemotherapy does not impair hypertrophy of the left liver after right portal vein obstruction. J Gastrointest Surg 2006;10:365–370
21. Parc Y, Dugué L, Farges O, Hiramatsu K, et al. Preoperative systemic 5-fluorouracil does not increase the risk of liver resection. Hepatogastroenterology 2000;47:1703–1705

22. Yedibela S, Elad L, Wein A, et al. Neoadjuvant chemotherapy does not increase postoperative complication rate after resection of colorectal liver metastases. Eur J Surg Oncol 2005;31:141–146
23. Aloia T, Sebagh M, Plasse M, et al. Liver histology and surgical outcomes after preoperative chemotherapy with fluorouracil plus oxaliplatin in colorectal cancer liver metastases. J Clin Oncol 2006;24:4983–4990
24. Sahajpal A, Vollmer CM, Dixon E, et al. Chemotherapy for colorectal cancer prior to liver resection for colorectal cancer hepatic metastases does not adversely affect peri-operative outcomes. J Surg Oncol 2007;95:22–27
25. Hewes JC, Dighe S, Morris RW, et al. Preoperative chemotherapy and the outcome of liver resection for colorectal metastases. World J Surg 2007;31:353–364
26. Pawlik TM, Olino K, Gleisner AL, et al. Preoperative chemotherapy for colorectal liver metastases: impact on hepatic histology and postoperative outcome. J Gastrointest Surg 2007;11:860–868
27. D'Angelica M, Kornprat P, Gonen M, et al. Lack of evidence for increased operative morbidity after hepatectomy with perioperative use of bevacizumab: a matched case-control study. Ann Surg Oncol 2007;14:759–765
28. Kooby DA, Fong Y, Suriawinata A, et al. Impact of steatosis on perioperative outcome following hepatic resection. J Gastrointest Surg 2003;7:1034–1044
29. Belghiti J, Hiramatsu K, Benoist S, et al. Seven hundred forty-seven hepatectomies in the 1990s: an update to evaluate the actual risk of liver resection. J Am Coll Surg 2000;191:38–46
30. Gomez D, Malik HZ, Bonney GK, et al. Steatosis predicts postoperative morbidity following hepatic resection for colorectal metastasis. Br J Surg 2007;94:1395–1402
31. Peppercorn PD, Reznek RH, Wilson P, et al. Demonstration of hepatic steatosis by computerized tomography in patients receiving 5-fluorouracil-based therapy for advanced colorectal cancer. Br J Cancer 1998;77:2008–2011
32. Sorensen P, Edal AL, Madsen EL, et al. Reversible hepatic steatosis in patients treated with interferon alfa-2a and 5-fluorouracil. Cancer 1995;75:2592–2596
33. Moertel CG, Fleming TR, Macdonald JS, et al. Hepatic toxicity associated with fluorouracil plus levamisole adjuvant therapy. J Clin Oncol 1993;11:2386–2390
34. Jones RJ, Lee KS, Beschorner WE, et al. Veno-occlusive disease of the liver following bone marrow transplantation. Transplantation 1987;44:778–783
35. Reiss U, Cowan M, McMillan A, et al. Hepatic veno-occlusive disease in blood and bone marrow transplantation in children and young adults: incidence, risk factors, and outcome in a cohort of 241 patients. J Pediatr Hematol Oncol 2002;24:746–750
36. Takayasu K, Muramatsu Y, Shima Y, et al. Hepatic lobar atrophy following obstruction of the ipsilateral portal vein from hilar cholangiocarcinoma. Radiology 1986;160:389–393
37. Makuuchi M, Thai BL, Takayasu K, et al. Preoperative portal embolization to increase safety of major hepatectomy for hilar bile duct carcinoma: a preliminary report. Surgery 1990;107:521–527
38. Azoulay D, Castaing D, Smail A, et al. Resection of nonresectable liver metastases from colorectal cancer after percutaneous portal vein embolization. Ann Surg 2000;231:480–486
39. Abdalla EK, Adam R, Bilchik AJ, et al. Improving resectability of hepatic colorectal metastases: expert consensus statement. Ann Surg Oncol 2006;13:1271–1280
40. Kubota K, Makuuchi M, Kusaka K, et al. Measurement of liver volume and hepatic functional reserve as a guide to decision-making in resectional surgery for hepatic tumors. Hepatology 1997;26:1176–1181
41. Shirabe K, Shimada M, Gion T, et al. Postoperative liver failure after major hepatic resection for hepatocellular carcinoma in the modern era with special reference to remnant liver volume. J Am Coll Surg 1999;188:304–309
42. Bouzari H, Amisano M, Zorzi D, et al. Hypertrophy of the future liver remnant volume following portal vein occlusion: portal vein embolization vs portal vein ligation. HPB 2006;8(suppl 2):27–28
43. Aussilhou B, Lesurtel M, Sauvanet A, et al. Right portal vein ligation is as efficient as portal vein embolization to induce hypertrophy of the left liver remnant. J Gastrointest Surg 2008;12:297–303
44. Gruenberger T, Tamandl D, Puhalla H, et al. Bevacizumab plus XELOX as neoadjuvant therapy for patients with potentially curable metastatic colorectal cancer. 2007 ASCO Annual Meeting Proceedings Part I. J Clin Oncol 2007; 25(suppl):4064
45. Engum SA, Sidner RA, Miller GA, et al. Early use of cisplatin is safe after partial hepatectomy. J Pediatr Surg 1993; 28:411–417