World Journal of Gastrointestinal Oncology

Online Submissions: http://www.wjgnet.com/1948-5204office
wjgo@wjgnet.com
doi:10.4251/wjgo.v2.i10.380

World J Gastrointest Oncol 2010 October 15; 2(10): 380-389
ISSN 1948-5204 (online)

EDITORIAL

Advances in therapeutics for liver metastasis from colorectal cancer

Akira Kobayashi, Shinichi Miyagawa

Akira Kobayashi, Shinichi Miyagawa, First Department of Surgery, Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto 390-8621, Japan
Author contributions: Kobayashi A collected and interpreted the data, and wrote the manuscript; Miyagawa S revised the manuscript.
Correspondence to: Shinichi Miyagawa, MD, PhD, Professor and Chairman, First Department of Surgery, Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto, Nagano 390-8621, Japan. shinichi@shinshu-u.ac.jp
Telephone: +81-263-372654 Fax: +81-263-351282
Received: July 30, 2010 Revised: September 15, 2010
Accepted: September 22, 2010
Published online: October 15, 2010

Abstract

The evolution of chemotherapeutic regimens that include targeted molecular agents has resulted in a breakthrough in the management of advanced colorectal liver metastasis (CLM), improving the progression-free survival after liver resection, and rendering initially unresectable liver tumors resectable, with reported resection rates ranging from 13% to 51%. In addition, the criteria used for selecting patients for hepatectomy have been expanding because of advances in surgical techniques and improvements in chemotherapy. However, the increasing use of chemotherapy has raised concern about potential hepatotoxicities such as steatosis, chemotherapy-associated steatohepatitis, and sinusoidal obstruction syndrome, and their deleterious effects on postoperative outcome. The present review focuses on the advantages and disadvantages of chemotherapy, strategies for the prevention and diagnosis of chemotherapy-associated liver injury, and the adoption of more aggressive surgical approaches, which have changed the traditional paradigm for CLM.

Key words: Colorectal liver metastasis; Chemotherapy; Hapatotoxicity; Multimodal therapy; Targeted biological agent

Peer reviewer: Oliver Stoeltzing, MD, Associate Professor, Department of Surgery and Surgical Oncology, Johannes Gutenberg University Hospital, Langenbeckstr. 1, Mainz 55131, Germany; Marc André Reymond, MD, MBA, Professor, Klinik für Allgemein-, Viszeral- und Thoraxchirurgie, Evangelisches Krankenhaus Bielefeld, Schildescher Str. 99, Bielefeld D-33611, Germany

Kobayashi A, Miyagawa S. Advances in therapeutics for liver metastasis from colorectal cancer. *World J Gastrointest Oncol* 2010; 2(10): 380-389 Available from: URL: http://www.wjgnet.com/1948-5204/full/v2/i10/380.htm DOI: http://dx.doi.org/10.4251/wjgo.v2.i10.380

INTRODUCTION

Approximately 50% of patients with colorectal cancer develop liver metastases at some point during the course of their disease[1,2]. Liver resection remains the treatment of choice for patients with resectable colorectal liver metastasis (CLM)[1]. However, the majority of patients with CLM are poor candidates for hepatectomy at presentation, and recurrence after surgery is common[3,4]. Hence, various combinations of chemotherapy and surgery have been evaluated in order to reduce the incidence of disease relapse and improve the long-term surgical outcome.

The efficacy of a combination regimen comprising fluorouracil/leucovorin (LV) with oxaliplatin and/or irinotecan has rendered initially unresectable CLM resectable after tumor downsizing, thus changing the prognosis significantly[5-9]. In addition, the combined use of targeted molecular therapies has further enhanced the efficacy of chemotherapy[10,11]. Recently, the impact of perioperative chemotherapy for initially resectable CLM was evaluated in a phase Ⅲ prospective randomized control trial[12]. However, the increasing use of chemotherapy has raised awareness of the potential hepatotoxicities of cytotoxic agents[13-17] and their possible deleterious effects on post-

operative outcome[16,17]. Furthermore, issues such as the optimum timing of surgery and the preoperative diagnosis of suspected chemotherapy-associated liver injury remain to be clarified.

In the 1980s, the features of CLM used conventionally to indicate the feasibility of liver resection were: a maximum of three nodules, absence of extrahepatic metastasis, and a clear resection margin of 10 mm[18]. Since then, however, the resectability criteria have been expanding because of advances in surgical techniques and perioperative care, as well as improvements in chemotherapy.

The present review focuses on the advantages and disadvantages of chemotherapy, strategies for the prevention and diagnosis of chemotherapy-associated liver injury, and the adoption of more aggressive surgical approaches, changing the traditional paradigm for CLM.

ADVANCES IN CHEMOTHERAPY

Advantages of chemotherapy

Chemotherapy for initially unresectable CLM: Although resection of CLM can offer a 5-year survival rate of 27%-40%[3,19-22], only 10%-20% of patients with CLM can be regarded as candidates for surgical resection because of the size and/or location of their tumors[5,23,24]. Hence, a major goal of chemotherapy for patients with initially unresectable CLM is to induce tumor shrinkage in order to increase the number who are eligible for radical resection. Recently, several reports have indicated that the improved efficacy of a combination regimen comprising fluorouracil/LV with oxaliplatin and/or irinotecan has rendered initially unresectable CLM resectable after tumor downsizing[5-9]. Reported resection rates, and R0 resection rates, have varied from 13% to 51%, and from 11% to 38%, respectively[25-33] (Table 1). The wide ranges may be attributable to the chemotherapeutic regimens employed, and also variations in the definition of resectability. For example, in some studies, the presence of at least five or six CLMs distributed diffusely in both lobes was defined as unresectable[8,9,26], whereas others did not consider this condition an absolute contraindication[21,34-36]. However, it is important to note that a proportion of patients with initially unresectable CLM were considered to become eligible for surgery by the same team, irrespective of the selection criteria adopted.

Only a few studies have examined the 5-year survival rate of patients with initially unresectable cancer whose lesions were rendered resectable by preoperative chemotherapy[5,25]. Adam *et al*[7] reviewed their 11-year experience of rescue surgery for 1439 patients with initially unresectable CLM, and showed that their strategy achieved 5- and 10-year survival rates of 33% and 22%, respectively, with a median survival period of 39 mo. These promising results were achieved through their aggressive surgical approach for frequent tumor recurrences: repeat hepatectomy was performed in 55% of patients with isolated hepatic recurrence and 51% of those with both hepatic and extrahepatic recurrence.

Perioperative or adjuvant chemotherapy for initially resectable CLM: Even after curative hepatectomy for CLM, cancer relapse will occur in the majority of patients[3,4]. In order to reduce the incidence of recurrence and to maximize overall survival, various combinations of chemotherapy and surgery have been evaluated, although a dilemma exists as to whether such cytotoxic agents should be administered before or after liver resection.

Prehepatectomy chemotherapy has been reported to have several theoretical advantages over surgery alone[37], including a higher rate of complete resection, ablation of micrometastases, provision of an indication of chemoresponsiveness, and identification of cases of aggressive disease. Indeed, several previous studies have shown that patients whose disease progressed while receiving chemotherapy had significantly shorter survival than those with stable or responsive disease, indicating that the response to chemotherapy before hepatectomy is a prognostic indicator[38-41]. However, despite the theoretical benefits of prehepatectomy chemotherapy, its impact on long-term outcome has not been clearly defined. A previous retrospective study[42] investigating the role of chemotherapy before hepatectomy for patients with 5 or more bilobar CLMs demonstrated that patients who received preoperative chemotherapy had a better 5-year survival rate than those who did not (38.9% *vs* 20.7%, P = 0.039). On the other hand, other studies have shown no survival benefit for patients who received prehepatectomy chemotherapy[41,43].

The use of adjuvant systemic chemotherapy with or without hepatic arterial infusion (HAI) after liver resection has been tested in several large randomized studies. Two studies demonstrated an improvement of progression-free survival after adjuvant chemotherapy, but no prolongation of overall survival[44,45]. Kemeny *et al*[46] reported a significant increase in the two year-survival of a group receiving combined therapy (surgery + systemic fluorouracil/LV + HAI) relative to a group receiving monotherapy (surgery + systemic fluorouracil/LV) (86% *vs* 72%, P = 0.03). However, a later update of their results showed that the median overall survival was comparable between the two groups (68 mo *vs* 59 mo, P = 0.10)[47]. Portier *et al*[48] reported a tendency for better disease-free and overall survival in a systemic chemotherapy group (fluorouracil/LV) than in a group receiving surgery alone, but the difference did not reach statistical significance because of insufficient power.

Nordlinger *et al*[12] evaluated the impact of perioperative chemotherapy for initially resectable CLM on the surgical outcome. In this phase Ⅲ prospective randomized control trial, 364 patients with up to four initially resectable CLMs were allocated to either six cycles of fluorouracil, LV, and oxaliplatin (FOLFOX4) given both before and after liver resection, or to surgery alone. The results showed the absolute increase in rate of progression-free survival at 3 years was 7.3% (P = 0.058) in randomized patients; 8.1% (P = 0.041) in eligible patients; and 9.2% (P = 0.025) in patients undergoing resection. Although the addition of perioperative chemotherapy did not significantly increase

Table 1 Resection rates and long-term outcomes following systemic chemotherapy in patients with unresectable metastatic colorectal cancer

Study	Treatment (*n*) Median survival (mo)	Resection rate (%) 5-year survival All/R0 (%)
Bismuth *et al*[5]	5-FU/LV ± oxaliplatin (330)	16/14
	NA	40[a]/-
Giacchetti *et al*[25]	5-FU/LV + oxaliplatin (151)	51/38
	48[a]/NR[b]	50[a]/58[b]
Wein *et al*[26]	5-FU/LV (53)	17/11
	NA	NA
Zelek *et al*[27]	5-FU/LV + irinotecan + HAI (31)	35/29
	-/20.2[b] (PFS)	-/65[b] (3-year survival)
Adam *et al*[7]	5-FU/LV + oxaliplatin and/or irinotecan (1104)	12.5/10.9
	39[a]/-	33[a]/-
Tournigand *et al*[28]	FOLFIRI (109)	9/7
	47[a]/-	NA
	FOLFOX4 (111)	22/14
	NR	NA
Pozzo *et al*[8]	FOLFIRI (40)	40/32.5
	14.3 (DFS)[a]/-	NA
Alberts *et al*[9]	FOLFOX4 (42)	40/33
	NA	NA
Seium *et al*[29]	5-FU/LV + oxaliplatin + irinotecan (30)	7/-
	NA	NA
Folprecht *et al*[30]	5-FU/LV + irinotecan + cetuximab (21)	-/19
	NA	NA
Masi *et al*[31]	FOLFOXIRI, simplified FOLFOXIRI (74)	-/26
	-/36.8[b]	-/37[b] (4-year survival)
Tournigand *et al*[32]	FOLFOX4 (311)	17.7/11.3
	38.9[a]/-	NA
	FOLFOX7 (309)	15.2/9.4
	43.0[a]/-	NA
Folprecht *et al*[33]	FOLFOX + cetuximab (53)	49/38
	NA	NA
	FOLFIRI + cetuximab (53)	43/30
	NA	NA

[a]Resected patients only; [b]R0 resection only. 5-FU/LV: 5-Fluorouracil/leucovorin; NA: Not available; NR: Not reached; HAI: Hepatic arterial infusion; PFS: Progression-free survival; FOLFIRI: 5-Fluorouracil, leucovorin, and irinotecan; FOLFOX: 5-Fluorouracil, leucovorin, and oxaliplatin; DFS: Disease-free survival; FOLFOXIRI: 5-Fluorouracil, leucovorin, oxaliplatin, and irinotecan.

the 3-year progression-free survival rate in intention-to-treat analysis, this initial study indicated that perioperative chemotherapy had the potential to reduce disease recurrence after liver resection in patients with CLM.

Whether patients with initially resectable CLM should receive perioperative or adjuvant chemotherapy should be examined in a prospective randomized trial comparing the two strategies.

Disadvantages of chemotherapy

Chemotherapy-associated liver injury: The increasing use of chemotherapy for CLM has raised awareness of the potential hepatotoxicities induced by cytotoxic agents and the effects of these drugs on postoperative outcome. Previous reports have indicated that preoperative administration of chemotherapeutic agents can be associated with pathological change in the liver, such as steatosis, chemotherapy-associated steatohepatitis (CASH), and sinusoidal injury[49-51].

Steatosis has been reported in 30%-47% of patients receiving systemic fluorouracil[52-54]. While the association between irinotecan-containing therapy and steatosis (> 30%) has been debatable[16,55,56], such therapy has been associated with an increased risk of steatohepatitis[16,55,56], which can progress to fibrosis, cirrhosis, and liver failure[51], and interestingly the risk was shown to be doubled in patients with a BMI of $\geqslant$ 25 kg/m^2 relative to those with a BMI of < 25 kg/m^2 (24.6% *vs* 12.1%, $P = 0.01$)[16].

Oxaliplatin-based chemotherapy is associated with sinusoidal injury, i.e. sinusoidal dilatation and hemorrhage related to disruption of the sinusoidal barrier, sinusoidal fibrosis, and veno-occlusive lesions[13-17]. The morphological features of the sinusoidal lesions are similar to those observed in veno-occlusive disease, recently renamed sinusoidal obstruction syndrome (SOS)[57].

Chemotherapy-associated liver injury and postoperative outcome: Kooby *et al*[58] reported that patients with steatosis, 58% of whom had received preoperative chemotherapy, showed a higher complication rate after hepatectomy than those without steatosis, and that the degree of steatosis was significantly correlated with total

and infective complications. These results were in line with those of other groups[59,60]. While the presence of steatosis rarely affects postoperative mortality[58], Vauthery *et al*[16] reported that patients with steatohepatitis had higher 90-d mortality than those without (14.7% *vs* 1.6%, $P = 0.001$).

With regard to sinusoidal injury, Nakano *et al*[17] showed that the postoperative complication rate after major liver resection was significantly higher in patients with sinusoidal injury than in those without (40% *vs* 6.3%, $P = 0.026$).

Preoperative chemotherapy and surgical outcome: While several studies have reported that preoperative chemotherapy was not associated with morbidity and mortality after hepatectomy[14,55,61-64], Karoui *et al*[15] demonstrated a higher morbidity rate after major liver resection in patients who had received preoperative chemotherapy. Similarly, Nordlinger *et al*[12] reported that the postoperative complication rate was significantly higher in a perioperative chemotherapy group than in a surgery-alone group (25% *vs* 16%, $P = 0.04$). In addition, two studies have shown that the number of cycles of chemotherapy administered was correlated with the incidence of postoperative complications[14,15].

Taken together, the data indicate that caution must be exercised when performing liver resection, especially major hepatectomy, for patients who have received a prolonged period of preoperative chemotherapy, irrespective of the treatment regimen.

Chemotherapy-associated liver injury: Prevention and diagnosis

Optimum duration of chemotherapy: For patients with initially unresectable CLM, the timing of surgery clearly depends on tumor downsizing, rendering patients eligible for liver resection. However, for patients with initially resectable CLM, the optimum duration of chemotherapy and the interval between chemotherapy and hepatectomy remain unresolved issues in the absence of any randomized trials.

The optimum duration of chemotherapy has been evaluated from the viewpoint of tumor response as well as the short-term results of surgery. White *et al*[65] showed that reduction of CLM became evident mainly within 4 mo from the start of induction systemic ± hepatic arterial infusion, with little further reduction thereafter. Based on these results, the authors recommended that surgery should be performed 2-4 mo from the induction of chemotherapy in patients whose disease responds to, or remains stable on, the therapy. Auer *et al*[66] reported that a radiological complete response (CR), albeit a rare event (3%-4%)[12,67], is not always a true CR as approximately one third of such patients show pathologically viable cancer cells or reappearance of the disease during follow-up. Importantly, the median time to CLM disappearance was 5 mo, and disappearance within 3 mo was observed in 25% of patients. Snoeren *et al*[68] suggested that liver resection could be considered after only three to four cycles of chemotherapy, so as not to lose the chance of identifying CLM intraoperatively.

Karoui *et al*[15] evaluated the influence of the number of chemotherapy courses on postoperative outcome, and showed that the risk of morbidity after major liver resection for CLM was higher in patients receiving 6 or more chemotherapy cycles than in those receiving less than 6 cycles (54% *vs* 19%, $P = 0.047$). Similarly, Aloia *et al*[14] reported that patients receiving more than 12 cycles of chemotherapy had a higher reoperation rate (11% *vs* 0%, $P = 0.04$) and a longer hospital stay (15 d *vs* 11 d, $P = 0.02$) than those receiving 12 courses or less. Although the chemotherapeutic regimens in these studies were heterogeneous (fluorouracil with or without irinotecan or oxaliplatin), the results suggested that a longer duration of preoperative chemotherapy could predispose some patients to operative risk.

Optimum interval between chemotherapy and hepatectomy: Discussion about the optimum interval between chemotherapy and hepatectomy has been based on the assumption that chemotherapy-induced hepatotoxicity is reversible. However, this has not yet been fully evaluated. Welsh *et al*[61] showed that the surgical complication rate was higher in patients with a shorter (4 wk or less) chemotherapy cessation period than in those with a longer interval (11%; *vs* 5.5% for an interval of 5-8 wk or 2.6% for an interval of 9-12 wk; $P = 0.009$). Nakano *et al*[17] showed that the time interval after chemotherapy was significantly shorter in patients with sinusoidal injury than in those without (3.6 mo *vs* 6.5 mo, $P = 0.048$). Takamoto *et al*[64] initially evaluated the recovery of liver function after the cessation of preoperative chemotherapy, and found a significant recovery of the indocyanine green retention rate at 15 min (ICGR15) at 2-4 wk after the last chemotherapy. These results support the contention that liver damage caused by chemotherapy is reversible after cessation. On the other hand, few studies have investigated the possibility of persistent liver damage. In a study by Rubbia-Brandt *et al*[13], some patients who underwent a second liver resection were found to have persistent SOS, which had been diagnosed at the initial hepatectomy, but had later progressed, even after discontinuation of chemotherapy. Similarly, Hubert *et al*[69] showed that moderate to severe SOS persisted for more than 6 mo after cessation of chemotherapy in one fourth of their patients. In a review article, Kopetz *et al*[70] stated that a limited course of chemotherapy, with an interval of at least 5 wk, might minimize the incidence surgical complications.

Diagnosis of chemotherapy-associated liver injury: Although CT or MRI is useful for imaging diagnosis of hepatic steatosis[71,72], it has been considered difficult to identify sinusoidal injury using imaging modalities. Ward *et al*[73] were the first to report that superparamagnetic iron oxide (SPIO)-enhanced T2-weighted gradient echo (GRE) imaging is effective for detecting sinusoidal injury. It

depicted areas affected by sinusoidal obstructive syndrome as reticular hyperintensity, and achieved a sensitivity of 87%, a specificity of 89%, a positive predictive value of 83%, and a negative predictive value of 92%.

In general, liver function tests have not been considered useful for diagnosis of chemotherapy-associated liver injury[49]. Nakano *et al*[17] reported that patients with sinusoidal injury after preoperative chemotherapy showed significantly poorer functional liver reserve, as evaluated in terms of ICGR15, than those without sinusoidal injury. In addition, multivariate analysis showed that a preoperative ICGR15 of > 10% was independently predictive of sinusoidal injury. Similar results were reported by Takamoto *et al*[64], who showed that the values of ICGR15 after chemotherapy were beyond the normal range. These results suggest that the ICG test could be a useful marker of not only chemotherapy-induced liver injury but also functional recovery of the liver from such injury.

Liver biopsy is a method for diagnosis of chemotherapy-induced liver injury, but it can yield false-negative information because of the heterogeneous nature of histological changes throughout the liver. Laparoscopy with direct inspection is another option for assessment of liver injury, although its value is limited to some extent because of its invasiveness and the qualitative nature of the information it provides[49,64].

Biological treatment

Optimum interval between the last chemotherapy and surgery: Targeted biological agents are being used increasingly for the treatment of CLM because of the improved survival they afford in combination with the standard fluorouracil-based chemotherapeutic regimen[11]. The anti-angiogenic effect of bevacizumab (BV), a monoclonal antibody against vascular endothelial growth factor (VEGF), has raised concern regarding the potential impact on bleeding and wound healing. In a previous pooled analysis, the incidence of grade 3 and 4 wound healing complications was higher in patients given preoperative BV than in those without, although the difference did not reach statistical significance (13% *vs* 3.4%, $P = 0.28$)[74]. It was noteworthy that no BV-treated patients experienced complications beyond 60 d from the last dose. These results have been supported by more recent studies demonstrating that BV can be administered preoperatively without an increase in morbidity after liver resection for CLM, provided the administration is stopped at 7-10 wk before surgery[75-77].

Since preclinical studies in mice have shown that VEGF also plays a pivotal role in liver regeneration after partial hepatectomy[78-81], it has been hypothesized that BV could impair liver regeneration. However, the effects of the agent have not yet been well clarified. Recently, two studies have presented data for liver regeneration after portal vein embolization[82-86] (PVE) or portal vein ligation (PVL) in patients receiving systemic chemotherapy with or without BV. One of them, conducted by the M.D. Anderson group[87], showed that preoperative chemotherapy with BV did not impair regeneration of the future remnant liver (FRL) when it was discontinued a median of 7 wk before PVE. The other study, by the Beaujon Hospital group[88], showed that the rate of hypertrophy was comparable between a non-BV-treated group and a BV-treated group given less than six cycles. Importantly, the latter study found that BV-treated patients receiving six or more cycles showed a far lower rate of hypertrophy than those given less than six cycles. In addition, no obvious increase in FRL was observed in elderly patients (≥ 60 years) who received six or more cycles of BV. The authors concluded that care should be taken when performing liver resection in patients who receive six or more cycles of BV and are ≥ 60 years of age.

Effect of BV on pathological response and background non-tumorous liver: The pathological effects of a preoperative BV-containing regimen on tumor viability or non-tumorous liver injury have not yet been evaluated in patients with CLM. The M.D. Anderson group[89] recently reported that the fluoropyrimidine-plus-oxaliplatin (5FU/OX) + BV regimen significantly reduced not only the extent of tumor viability (32.9% *vs* 45.3%, $P = 0.02$), evaluated as the area of residual viable cancer cells on hematoxylin and eosin-stained sections, but also both the incidence and severity of sinusoidal dilatation (any grade: 27.4% *vs* 53.5%; moderate or severe: 8.1% *vs* 27.9%; both $P < 0.01$) in comparison with a 5FU/OX-only group. One possible explanation for the protective effect of BV against OX-induced SOS is blockade of VEGF[89], as VEGF plays a critical role in the development of SOS: patients with SOS show a higher serum VEGF level, and extent of the increase parallels the clinical severity of SOS[90].

Selective internal radiotherapy

Radioembolization, also termed selective internal radiotherapy (SIRT), is a technique for administering internal radiotherapy to unresectable CLM by injecting resin or glass microspheres containing[90]. Yttrium into the hepatic artery[91,92].

Several clinical trials of SIRT concomitant with radiosensitizing systemic chemotherapy have obtained promising results. A recent phase I-II study has shown that SIRT can be given with FOLFOX4, achieving acceptable toxicity, a radiological response rate of 90%, and a progression-free survival of 9.3 mo[93]. An ongoing large phase Ⅲ trial investigating 5-FU, oxaliplatin and folinic acid with or without SIRT as a first-line treatment for patients with CLM will provide important data on the efficacy and toxicity of this combined modality approach[94].

ADVANCES IN SURGERY

Since Ekberg *et al*[18] proposed three eligibility requirements for liver resection of CLM – fewer than 4 liver tumors, no extrahepatic disease, and a resection margin of at least 10 mm - these limitations have been challenged by various

surgeons, leading to more aggressive approaches to the treatment of CLM.

Approaches for extending the criteria for liver resection

Staged hepatectomy: Curative hepatectomy has been abandoned in certain patients with bilobar multiple CLM, even after systemic chemotherapy and portal vein embolization. The Paul Brousse group[36] were the first to report planned two-stage hepatectomy for such patients, consisted of initial hepatectomy removing the greatest number of CLM as possible, followed by chemotherapy, and a second hepatectomy for any remaining tumors. The timing of the second hepatectomy is decided after confirming the following criteria: adequate parenchymal regeneration, control of any remnant CLM by chemotherapy, and probability of radical resection. This approach yielded a 3-year survival rate of 35% and a median survival period of 31 mo after the second hepatectomy in highly selected patients. However, the results were hampered by a 15% mortality rate after the second resection, probably because of the detrimental effects of prolonged chemotherapy.

An alternative staged procedure for patients with synchronous CLM was reported by the Beaujon group[35]. This consisted of removal of the primary tumors and all left-sided metastases with simultaneous right portal vein ligation as the first step, and a right or extended right hepatectomy after hypertrophy of the left hemi-liver as a second step. They applied this strategy to 20 patients (12 with colorectal cancer and 8 with neuroendocrine tumors), and eventually 14 patients (70% of the total population) underwent right hepatectomy (n = 8) and extended right hepatectomy (n = 6) without major complications including liver failure. Jaeck *et al*[34] reported their experience of a two-stage procedure combined with portal vein embolization for patients with initially unresectable CLM. PVE *via* a percutaneous approach was scheduled 2 to 5 wk after the first hepatectomy. They performed 12 right hepatectomies and 13 extended right hepatectomies with no mortality, and the long-term survival was comparable with that for patients with initially resectable CLM.

Hepatic pedicle lymphadenectomy: Hepatic pedicle lymph node (HPLN) metastasis has been reported to be the most significant prognostic factor affecting long-term outcome after liver resection for CLM[18,21,95-100], and celiac axis nodal involvement has been defined as an absolute contraindication for liver resection[101]. Jaeck *et al*[102] have routinely performed hepatectomy concomitant with complete HPLN dissection in patients fulfilling at least one of the following criteria: 3 or more liver metastases, location in segment 4 or 5, and a high preoperative CEA level. Their procedure conferred a survival benefit only when the HPLN metastases were limited to area 1 (hepatoduodenal ligament and retroduodenopancreatic nodes). Recently, they evaluated the impact of HPLN dissection on long-term outcome in the era of multi-agent chemotherapy. Their strategy yielded an overall 5-year survival rate of 17.3% and a median survival period of 20.9 mo without any increase of postoperative mortality and morbidity. Surprisingly, the extent of HPLN involvement, in either area 1 or 2 (along the common hepatic artery and celiac axis) or both, did not affect overall survival after surgery. They concluded that HPLN dissection may offer a survival benefit provided that the resection is potentially curative and followed by adjuvant chemotherapy[103].

Microscopically positive resection margin: Several previous studies addressing the issue of the surgical margin (SM) have yielded conflicting results. Some reports have recommended a SM wider than 1 cm because of its association with prolonged survival in comparison with subcentimeter resections[18,104-107]. However, other studies have shown that a margin of less than 1 cm has no significant impact on survival, as long as the margin is cancer-negative[108-110]. Whereas most these studies were based on statistical analysis of prognostic factors, Kokudo *et al*[110] carried out a histological and genetic assessment of K-ras and *p53* gene mutations to identify the minimum margins in surgically resected specimens. Histological micrometastases were found in one fourth of the patients, and the genetic analyses added 3 more cases of micrometastases. In addition, all of these micrometastases were detected within 5 mm of the tumor border. Cut-end recurrence was observed in 20% of patients with a surgical margin of < 2 mm, whereas the incidence was about 6% in those with margins ranging from 2 to 9 mm. On the basis of these results, the authors proposed that a surgical margin of 2 mm was an acceptable minimum requirement.

Because many previous studies have agreed that microscopic infiltration of the resection margin, defined as R1 resection, is a significant factor affecting survival[3,106,108,109,111,112], inability to achieve a cancer-free surgical margin has been considered an absolute or relative contraindication for hepatectomy. The Paul Brousse group[113] analyzed the necessity of achieving negative histological margins. Although cancer tended to recur more often in the R1 group, the long-term outcomes were similar to those observed after R0 resection, in spite of the higher number of tumors, larger tumor size, and more frequent bilobar distribution in the R1 group than in the R0 group. The authors attributed these promising results to their aggressive strategy, consisting of pre- and postoperative chemotherapy, repeat resection, and routine application of argon beam or bipolar coagulation to the cut surface of the liver.

CONCLUSION

Advances in both chemotherapy and liver surgery have expanded the pool of candidates for potentially curative hepatectomy for CLM. Recognition of chemotherapy-induced liver injury further emphasizes the need for multi-disciplinary approaches to maximize treatment efficacy

with minimum hepatotoxicities and morbidity. The issue of whether patients with initially resectable CLM should receive perioperative or adjuvant chemotherapy needs to be addressed with a prospective randomized trial comparing the two strategies.

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