Clinicopathological analysis of recurrence patterns and prognostic factors for survival after hepatectomy for colorectal liver metastasis

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Abstract

Background
Hepatectomy is recommended as the best effective therapy for liver metastasis from colorectal cancer (CRCLM). It is crucial to elucidate the prognostic clinicopathological factors.

Methods
Eighty-three patients undergoing initial hepatectomy for CRCLM were retrospectively analyzed with respect to tumor characteristics of primary colorectal and metastatic hepatic tumors, operation details and prognosis.

Results
The overall 5-year survival rate after initial hepatectomy for CRCLM was 57.5%, and the median survival time was 25 months. Univariate analysis clarified that the significant prognostic factors for poor survival were the depth of primary colorectal cancer (≥ serosal invasion), hepatic resection margin (< 5 mm), presence of portal vein invasion of CRCLM, and the presence of intra- and extrahepatic recurrence. Multivariate analysis indicated the presence of intra- and extrahepatic recurrence as the independent predictive factors for poor prognosis. The risk factors for intrahepatic recurrence were resection margin (< 5 mm) of CRCLM, while no risk factor for extrahepatic recurrence was noted. In subgroup with synchronous CRCLM, combination of surgery and adjuvant chemotherapy controlled intrahepatic recurrence and improve the prognosis significantly.

Conclusions
Optimal surgical strategies in conjunction with effective chemotherapeutic regimens need to be established in patients with risk factors for recurrence and poor outcome listed above.
Background

Despite the recent improvement in the diagnosis and management of colorectal cancer (CRC) which has enabled early detection followed by early treatment, still many advanced cases with hepatic or peritoneal metastasis are encountered. For further improvement of the prognosis of CRC, it is particularly important to prolong the survival of these advanced cases with distant metastasis.

Hepatectomy for liver metastasis from colorectal cancer (CRCLM) is recommended as the best effective therapy [1-11]. However, to date, 50% to 75% of patients develop a recurrence of the disease after curative resection of CRCLM. Moreover, the curative rate by initial hepatectomy is only 20% to 30% of cases [4-6, 12]. Factors associated with recurrence and prognostic determinants after the initial hepatectomy are still controversial. Recently, many studies reported that the duration of survival is markedly prolonged by effective chemotherapies, including the molecular target drugs, for unresectable or recurrent condition of colorectal cancer [13, 14]. Therefore, it is necessary to elucidate predictive factor(s) relevant to recurrence and survival, to determine optimal treatment strategies for each patient with CRCLM.

The aim of this study is to retrospectively investigate surgical outcomes in a consecutive series of patients undergoing hepatectomy for CRCLM at a single institution, in order to analyze recurrence patterns and clinicopathological prognostic factors for survival.

Methods

Patient selection:

A retrospective study was conducted on consecutive 85 patients undergoing initial hepatectomy for CRCLM for curative intent at Osaka Medical College Hospital from
1995 to 2008. Clinical records and follow-up data were obtained for 83 patients. Perioperative mortality was not observed in patients of this study. There were 55 men and 28 women. The average age at the initial hepatectomy was 66.5±10.4 years (range, 29-87 years). The mean observation period was 62.8 months (range, 4-129 months).

**Characteristics of colorectal cancer:**

The primary tumor was in the colon in 60 cases (72.3%) and in the rectum in 23 cases (27.7%). Among the patients with CRC, tumors were located on right in 13 (15.7%), transverse in 9 (10.8%), left colon in 38 (45.8%). Sixty-three percent of the primary tumors had involved regional lymph nodes, and 46.8%, 51.9% had well- or moderately-differentiated histology, respectively. The histological depth of invasion in the colorectal wall is denoted as follows: se, serosa; ss, sub-serosa; a1, sub-adventitia; a2, adventitia. In 58 patients (71.6%), the depth of the primary tumors was within subserosal layer (≤ ss (a1)) of the colorectal wall.

**Hepatectomy:**

In this series, we currently indicate hepatectomy for CRCLM when the following 3 conditions are met: (1) the primary CRC was curatively resected; (2) metastasis is located only in the liver; (3) no limitation regarding the number or size of CRCLM as far as hepatic functional reserve is warranted after hepatectomy. All hepatectomy was performed by three experienced hepatobiliary surgeons (MH, FH, and NT) during the study period. All patients received potentially curative hepatectomy with removal of gross tumor with negative macroscopic margin. With respect to hepatic hilar lymph nodes, we do not routinely perform lymph node dissection, since node-positive cases in this region were strongly associated with extremely poor survival in our previous experience (data not shown).
Synchronous (as opposed to metachronous) CRCLM was defined as simultaneous presentation of liver metastasis at the time of CRC operation, and was detected in 28 patients (33.7%). They received either synchronous or metachronous hepatectomy, mainly based on the each patient’s condition and emergency needed.

In principal, partial or non-anatomical hepatectomy was performed, whereas systemic or anatomical hepatectomy was preferred in cases when this procedure had advantage in terms of operation time, blood loss, safety, and invasiveness. Hepatic resection was performed following the standard technique as previously reported [15]. An ultrasonic dissector (SonoSurg system; Olympus Inc., Tokyo, Japan) was used for parenchymal transection, and small vessels were ligated or coagulated using soft-coagulation system or bipolar electrocautery. During the resection procedure, surgical margin was carefully confirmed using intraoperative ultrasonography in order to obtain surgical margin of 5-10 mm in general as possible. Thus, in 63.6% of cases, hepatic surgical margin was wider than or equal to 5mm.

Chemotherapy:

With respect to the chemotherapy before hepatectomy and adjuvant chemotherapy after hepatectomy, the eligibility criteria in this series included histologically-proven adenocarcinoma of the colon or rectum. Patient criteria included an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2. Additionally, patients had to have no serious or uncontrolled concurrent medical illness; no active infection; adequate hematologic parameters (WBC > 4.0×10³/L, platelet count > 100×10⁹/L), renal functions (serum creatinine ≤ 1.2 mg/dl or calculated creatinine clearance by Cockcroft formula ≥ 50 ml/min), or hepatic functions (total bilirubin < 2.0 mg/dl and aspartate aminotransferase, alanine aminotransferase < 100 IU/L).

Regimens consisted of 5-Fluorouracil (5-FU) alone, 5-FU/leucovorin (LV), 5-
FU/cisplatin, tegafur plus uracil (UFT) alone, UFT/LV, oteracil (TS-1), FOLFOX (infusional 5-FU/LV + oxaliplatin), FOLFIRI (infusional 5-FU/LV + irinotecan) and IFL (5-FU/LV + irinotecan). Thus, 35 patients (42.2%) received the chemotherapy before hepatectomy and 56 patients (71.8%) received the adjuvant chemotherapy after hepatectomy.

Patients follow-up:

Patients were examined for CRCLM recurrence by ultrasonography and contrast enhanced computed tomography (CT) every 4-6 months and blood tests including tumor markers such as carcinoembryonic antigen (CEA), every 2-3 months after discharge. When recurrence was suspected, magnetic resonance imaging (MRI) was performed to ensure the appearance of new lesions in the remnant liver, while systemic recurrence was examined by fluorodeoxyglucose-positron emission tomography (FDG-PET) or Gallium scintigram. Chest and pelvic CT was also performed principally every 6 months for local and pulmonary metastasis or recurrence. Recurrence was diagnosed when at least two imaging studies confirm the new lesions showing typical features of CRC/CRCLM, comparing with the previous images. The recurrent CRCLM were treated by repeat hepatectomy when applicable (n=15), otherwise by systemic chemotherapy, or their combination.

Clinicopathological analysis:

Patient demographics, laboratory tests including tumor markers, tumor characteristics, treatment, recurrence, and survival data were analyzed to determine prognostic factors in terms of survival rate at 3- and 5-years after the initial hepatectomy for CRCLM. The surgically resected specimens were studied macro- and microscopically to determine the various tumor characteristics including size of the largest tumor, number, morphology, extent of the tumor, and surgical margin. For
microscopic analysis, the resected specimens were fixed in 10% formaldehyde and sliced into 5-mm section. After each section was sliced into 5-µm tissue sections and stained with hematoxylin and eosin, two specialists of pathology (YS, AT) reviewed for histological confirmation of the pathological diagnosis. In this study, surgical margin status was defined as the distance of the lesion(s) closest to the cut surface of the liver, and macroscopically classified into two categories: a surgical margin of 5 mm or wider (≥ 5 mm), and narrower than 5 mm (< 5 mm).

Statistical analysis:

Actuarial survival rate was calculated by the Kaplan-Meier method. Univariate analyses were performed using the log-rank test. Multivariate analyses were performed by Cox proportional hazards regression. Statistical comparisons were made by Fisher’s exact probability test. A difference was regarded as statistically significant at $P < 0.05$.

Results

Primary colorectal tumor characteristics:

Tumor characteristics of primary CRC were analyzed for prognostic values (Table 1). Included were: tumor location (colon or rectum), tumor differentiation (well, moderately, or poorly differentiated adenocarcinoma), number of lymph nodes metastasis, depth of tumor invasion in the colorectal wall (≤ ss (a1) or ≥ se (a2); ss, sub-serosa; se, serosa; a1, sub-adventitia; a2, adventitia), lymphatic invasion, venous invasion, and Duke’s stage; the only significant difference in survival rate was observed between patients with primary CRC ≤ ss (a1) and those with ≥ se (a2) in the colorectal wall ($P = 0.0133$).

Time of liver metastasis and timing of hepatectomy:
Among 83 patients receiving hepatectomy for CRCLM, 13 (15.7%) patients received synchronous liver and colorectal resection, and 70 (84.3%) patients received metachronous resection (Table 1). The survival rate at 3- and 5- year was 70.5% and 70.5% in 13 patients with synchronous resection, 61.5% and 55.2% in 70 patients with metachronous resection. No differences in survival rates between these two groups were noted ($P = 0.4927$).

Synchronous CRCLM was detected at the time of CRC operation in 28 patients (33.7%). They underwent hepatectomy synchronously in 13 and metachronously in 15 patients. The survival rate at 5-year was 70.5% in 13 patients with synchronous resection, and 54.2% in 15 patients with metachronous resection. No difference in survival rates between these two groups was noted ($P = 0.6547$). Also, timing of hepatectomy was not associated with intra- and extrahepatic recurrence ($P = 1.0000$).

**Metastatic liver tumor characteristics:**

The mean and the median size of the largest metastatic lesions were 3.58±1.93cm and 3.0cm, respectively. Of 83 patients, 47 patients (56.6%) underwent resection for solitary metastasis, 27 patients (32.5%) for 2 or 3 tumors, and 9 patients (10.8%) had 4 or more tumors resected (Table 1). In 63 patients (75.9%), the tumor location was unilobar (right in 36, left in 27), and 20 patients (24.1%) had bilobar disease resected. There were no significant differences in terms of the number, maximal size, and distribution of CRCLM ($P = 0.3868$, 0.9255, and 0.1882, respectively). The serum value of CEA immediately before hepatectomy was not associated with subsequent survival rate. Portal vein invasion was observed in 8 patients (9.8%) with the significantly worse 3- and 5-year survival when compared with those without portal invasion (28.6% and 0% vs. 66.2% and 63.4%, respectively, $P = 0.0074$; Fig. 1).
However, there was no significant correlation between portal vein invasion and intrahepatic recurrence rate ($P = 0.7072$).

**Operation-related parameters:**

With regard to the type of hepatectomy (anatomic, 44; non-anatomic, 39) and extent of resection (< lobectomy, 62; ≥ lobectomy, 21), no differences in survival rates between these groups were noted ($P = 0.4862, 0.0875$, respectively, Table 1).

Compared with the patients with a hepatic surgical margin $\geq 5$ mm (n = 49, 63.6%), the 3- and 5-year survival rate for those with resection margin $< 5$ mm (n = 28, 36.4%) was significantly worse ($\geq 5$mm vs. $< 5$mm, 70.4% and 64.5% vs. 47.8% and 41.8%, respectively $P = 0.0399$; Fig. 2). During hepatic parenchymal resection, tumors were exposed on the cut surface of the liver in 6 patients (7.3%), however, the survival of those patients was not significantly different from the other patients without tumor exposure.

**Intra- and extrahepatic recurrence after initial hepatectomy:**

Recurrence was detected in 52 (65.0%) of the patients who underwent hepatectomy (Table 1). The site of the first recurrence was the liver in 32 (41.0%) patients. Twenty-six (32.5%) patients had extrahepatic recurrence; the lung in 18, the peritoneal cavity or local recurrence in 9, the brain in 2, and the bone in 1. Patients with recurrent hepatic metastasis after initial hepatectomy (n = 37, 44.6%) had a significantly worse survival than those without hepatic recurrence (n= 46, 55.4%, $P = 0.0104$). Also, patients with recurrent extrahepatic metastasis after initial hepatectomy had a significantly worse survival than those without extrahepatic recurrence ($P = 0.0217$). Especially, those with lung metastasis after hepatectomy had extremely poor survival (3 year, 39.9%; 5 year, 0%).
We also analyzed the risk factor for intra- and extrahepatic recurrence. On uni- and multivariate analysis, hepatic resection margin (< 5mm) was significantly associated with intrahepatic recurrence after initial hepatectomy ($P = 0.0133$; **Table 2**). No significant risk factor for extrahepatic recurrence was identified (data not shown).

**Perioperative chemotherapy:**

Thirty-five patients (42.2%) received chemotherapy before initial hepatectomy, and 56 patients (71.8%) received chemotherapy after hepatectomy. Overall, the presence or absence of chemotherapy, regardless of the chemotherapies before or after hepatectomy, or their combination, was not associated with intra- or extrahepatic recurrence or survival (**Table 1, 2**). In subgroup analysis, in 55 patients with metachronous CRCLM, the chemotherapies before and/or after hepatectomy was not associated with recurrence or the prognosis (**Table 3a, 4a**). On the contrary, in 28 patients with synchronous CRCLM, adjuvant chemotherapy after hepatectomy was significantly associated with lower intrahepatic recurrence rate ($P = 0.0087$) and the better prognosis ($P = 0.0458$) after initial hepatectomy, but not for extrahepatic recurrence (**Table 3b, 4b**).

**Patient survival and prognostic factors:**

The survival time of the patients ranged from 4 months to 129 months, the mean survival time was $36.5 \pm 28$ months, and median survival time was 25 months. The 5-year survival rate for the 83 patients after initial hepatectomy was 57.5%, which is comparable to reported survival rate of 20% to 58% [4, 6-8, 10-12, 16, 17]. The prognostic factors analyzed are shown in **Table 1**. On univariate analysis, tumor depth of CRC ($\leq ss (a1)$ vs. $> se (a2)$), portal vein invasion of CRCLM, macroscopic hepatic resection margin ($< 5mm$ vs. $\geq 5mm$), and the presence of intra- and extrahepatic recurrence were associated with a significant difference in survival rate after initial
hepatectomy (P = 0.0133, 0.0074, 0.0399, 0.0104, and 0.0217, respectively, Table 1, Figure 3). Multivariate analysis revealed that independent prognostic factors for poor outcome were the presence of intra- and/or extrahepatic recurrence (P = 0.0051, 0.0064, respectively, Table 1).

Discussion

While untreated CRCLM has a poor prognosis with median survival ranging from 6 to 12 months and cannot be expected the survival over 5 years, long-term survival and potential for cure following surgical resection for CRCLM had been demonstrated in numerous uncontrolled studies [7, 8, 12]. They reported that the overall 5-year survival rates are in the range of 20% to 58% and the median survival times are 24-46 months [4, 6-8, 10-12, 16, 17]. However, it is also reported that 57% to 78% of those patients will develop a recurrence of the disease in the hepatectomy series, and intrahepatic recurrence occurs in approximately 50% [4, 6, 9, 18]. It has been considered that occult metastasis surfacing from the primary CRC and residual lesion scattered from liver metastasis are the two major pathways through which hepatic recurrence of metastatic lesion occurs after initial hepatectomy [19, 20]. Therefore, treatment strategies including hepatic resection should be determined on the basis of these mechanisms for recurrence of metastasis. In Japan, surgical procedures for CRCLM is recommended if the following conditions are met: (1), the primary tumor was curatively resected; (2), metastasis is located only in the liver; (3), the patient is in condition to be able to bear hepatectomy; and relative indications include: (4), extrahepatic metastasis can be controlled when exists; (5), reductive operation has a meaning as a part of multimodal treatment [21]. However, the detailed consensus in terms of ideal timing, type, and extent of hepatectomy and optimal combination with perioperative chemotherapy are not currently provided with
sufficient evidences. The aims of this study are to retrospectively evaluate the significant prognostic factors for survival and risk factors for recurrence in patients who underwent hepatectomy, and thereby to determine the optimal timing and method of hepatectomy with concurrent use of perioperative chemotherapy.

In the present study, the prognostic factors on univariate analysis were the depth of the primary CRC, portal vein invasion and surgical margin at hepatectomy for CRCLM, and the presence of intra- and extrahepatic recurrence after the initial hepatectomy. The independent prognostic factors on multivariate analysis were the presence of intra- and extrahepatic recurrence. Of these factors, the portal vein invasion and surgical margin status at hepatectomy are important factors through which surgery can improve prognosis.

There are several literatures reporting the risk factors of intra- and extrahepatic recurrence [7, 22, 23, 24]. In our study, independent risk factor for intrahepatic recurrence was the hepatic resection margin, while there was no risk factor regarding extrahepatic recurrence. Hematogenous dissemination of CRC was reported to be significantly associated with the size of liver metastatic nodules by cascade theory [25]. In this theory, in accordance with the process of CRCLM metastasizing to the lung, and subsequently to the other organs, the size of CRCLM is thought to increase. However, our study implicated that recurrence occurs by surfacing micrometastasis from the primary CRC which could not be detected perioperatively, since observed risk factor for intra- or extrahepatic recurrence did not include the size or number of CRCLM.

The surgical margin of < 5mm at hepatectomy was detected as a risk factor for subsequent intrahepatic metastasis in this study. The role of surgical margin status as a prognostic factor to predict posthepatectomy survival has been controversial [24, 26,
and in the largest single-center series, Are et al. reported that margin width > 1 cm is an independent predictor for better survival and so is optimal [28]. Nuzzo et al. also recently reported histological surgical margin ≤ 5 mm was associated with lesser overall and disease-free survival rates independent of other clinic-pathologic factors [29]. In contrast, Bodingbauer et al. demonstrated that the rate of recurrence at the surgical margin was low and a positive margin was not associated with an increased risk of recurrence either at the surgical margin or elsewhere, if hepatectomy is performed with ultrasonic dissector by experienced surgeons [24]. The current study is distinct from the previous studies in terms of macroscopic, instead of histological, surgical margin utilized as a parameter. We adopted macroscopic surgical margin rather than microscopic margin, since 1) we considered that use of various dissection and coagulation devices such as soft-coagulation system, ultrasonic dissector, and bipolar electrocautery during hepatic parenchymal transection [15], would potentially hinder an accurate assessment regarding pathological surgical margin status including R0 (no residual tumor) and R1 (microscopic residual tumor) status [24, 29]; 2) we considered the macroscopic surgical margin as a better parameter of clinical usefulness for patient and treatment selection. Namely, during the preoperative evaluation, whether surgical margin ≥ 5mm is macroscopically feasible or not, would be utilized as a practical marker to determine which is indicated first, either hepatectomy or neoadjuvant chemotherapy as an initial therapy for each patient. If surgical margin is estimated less than 5mm, preoperative chemotherapy would be the optimal option [30], though it needs to be noted that resection should not be precluded whatever the width of the surgical margin, since no other single treatment modality can surpass hepatectomy even with 0-1 cm surgical margin [28]. In the present study, surgical margin status was
determined as a prognostic factor on univariate, but not on multivariate analysis, which is in accordance with the report by Kokudo et al. that surgical margin was correlated with tumor recurrence but not with survival rate [26]. However, when insufficient surgical margin is suspected during hepatectomy, or postoperative pathology of the resected specimen reveals inadequate surgical margin, adjuvant chemotherapy should be started to prevent intrahepatic recurrence, though prospective study on this approach is necessary to make a conclusive remark.

Portal vein invasion in the resected liver was observed in a small number of patients (9.8%), but also showed significant negative impact on survival, suggesting it would be reflecting the grade of aggressiveness and invasiveness of each tumor, or potential for intrahepatic micrometastases, as implicated by some authors [29, 31] in the context of surgical margin status as a surrogate marker for malignant potential. Therefore, optimal surgery should include strategy against portal vein invasion, such as anatomical hepatic resection including Glisson’s sheath with sufficient margin, and aggressive adjuvant chemotherapy for this subgroup of patients [32], yet further studies are needed to clarify its clinical significance.

Regarding the timing of hepatectomy for synchronous CRCLM, there has been a rebuttal on whether to perform simultaneous resection or to put an observation period for a couple of months. We did not detect any difference between these two approaches, suggesting that in case of synchronous situation, surgery should be planned at least before hepatic tumor(s) to become unresectable and patients need to be treated with adjuvant chemotherapy immediately, since this subgroup appeared to be benefitted from adjuvant chemotherapy. There is not yet sufficient consensus as to whether the perioperative chemotherapies are significantly associated with the disease-free survival or the
prognosis [33]. In our data, only in subgroup with synchronous CRCLM, combination of surgical therapy and adjuvant chemotherapy after hepatectomy could control intrahepatic recurrence and consequently improve the prognosis significantly. Conversely, in case of patient subgroup having synchronous CRCLM, adjuvant chemotherapy would be essential. As for metachronous disease, we could not detect benefits of chemotherapy in this study; however, it should be noted that these chemotherapies in the present series mainly depended on UFT + LV, TS-1, FOLFOX and FOLFIRI, and the recent molecular targeting agents such as bevacizumab and cetuximab, which has been reported to improve the prognosis of recurrent and unresectable CRC [14, 34,35,36], were not included in this study. Since these newer chemotherapies before hepatectomy are expected to control a recurrence by extermination of the micro cancer cell, we are currently conducting a similar study on those patients who received these chemotherapeutic agents.

Conclusions

In CRCLM, intra- and extrahepatic recurrence are the independent prognostic factors, and the independent risk factors for intrahepatic recurrence included macroscopic resection margin during hepatectomy. Combination of surgery and adjuvant chemotherapy for synchronous CRCLM could control intrahepatic recurrence and significantly improve the prognosis. Considering the outcomes of treatment for CRCLM are not yet satisfying, extermination of the micro cancer cell should be achieved by introduction of more potent chemotherapeutic agents in combination with optimal surgery would be required. Further study is needed to clarify this matter.
Competing interests
The authors declare that they have no competing interests.

Authors' contributions
MH conceived the study concept and design, was involved with patient care and
drafted the manuscript and literature review. YI, KK, TS, MA, FH, YM, JO, AT, and
YS were involved with formation of the study concept and design, patient care and
drafting of the manuscript and literature review. NT carried out the operation on the
patient and was the main contributor in the writing of the manuscript. All authors
have read and approved the final version of the manuscript. Please see sample text in
the instructions for authors.

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Figures

**Figure 1** - Survival curves according to portal vein invasion in the resected liver specimen.

No portal vein invasive disease is denoted as “port (-)”. Invasion confined to the portal vein is arbitrarily designated as “port (+)”. Portal vein invasion was observed in 8 patients with the significant worse 3- and 5 year survival when compared with those without portal invasion (28.6% and 0% vs. 66.2% and 63.4%, respectively, *P* = 0.0074).

**Figure 2** - Survival curves according to surgical margin in the resected liver specimen.

A surgical margin of 5mm or wider is denoted as “≥ 5 mm”. A surgical margin narrower than 5mm is denoted as “< 5 mm”. Patients with a surgical margin of 5mm or wider had a better survival rate than those with a narrower resection margin (*P* = 0.0399).
**Figure 3** - Survival curves according to the presence of intrahepatic recurrence after the initial hepatectomy.

The presence of recurrence is denoted as “(+)” and absence “(-)”. The presence of intrahepatic recurrence were associated with a significant difference in survival after initial hepatectomy ($P = 0.0104$).

**Figure 4** - Survival curves according to the presence of extrahepatic recurrence after the initial hepatectomy.

The presence of recurrence is denoted as “(+)” and absence “(-)”. The presence of extrahepatic recurrence were associated with a significant difference in survival after initial hepatectomy ($P = 0.0217$).

**Tables**

**Table 1** - Analysis of clinicopathological factors for prognosis

CRC: colorectal cancer, CRCLM: liver metastasis from colorectal cancer, CEA: carcinoembryonic antigen.

**Table 2** - Risk factors for intrahepatic recurrence after initial hepatectomy

CRC: colorectal cancer, CRCLM: liver metastasis from colorectal cancer.

**Table 3** - Effect of peri-operative chemotherapy on survival for (a) metachronous and (b) synchronous CRCLM

**Table 4** - Effect of peri-operative chemotherapy on recurrence for (a) metachronous and (b) synchronous CRCLM
Figure 2
Additional files provided with this submission:

Additional file 1: table1,BMCS.doc, 130K
http://www.biomedcentral.com/imedia/1986047900395724/supp1.doc
Additional file 2: table2,BMCS.doc, 74K
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Additional file 3: table3,BMCS.doc, 53K
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Additional file 4: table4,BMCS.doc, 53K
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