125 mg/m^2 or 150 mg/m^2 of irinotecan weekly would probably result in decreased dose intensity due to severe adverse events. Therefore, we firmly believe that our RD is adequate for Japanese patients.

In our study, only one patient had grade 3 febrile neutropenia as the DLT. This patient had a slightly abnormal bilirubin level 1 week before study entry. The investigator in charge enrolled this patient because the serum bilirubin level had returned to normal at the time of entry. Knight et al.[9] analyzed predictors of toxicity in patients given the original Saltz regimen. Their logistic regression analysis showed that only an elevated bilirubin level predicted a higher incidence of grade 4 neutropenia (P 0.03). They concluded that dose attenuation was most rapid in patients with performance status 2 and abnormal baseline bilirubin. In patients with mildly elevated bilirubin levels, systemic exposure to irinotecan and SN-38 increases the levels considerably, because the pharmacokinetics of irinotecan depend on liver function; dose reduction is therefore required.[2,9] Wasserman et al.[14] reported that patients with Gilbert's syndrome were at increased risk for irinotecan-related toxicity because of deficient UGT*1.1 activity. We recommend that treatment with irinotecan is started at a dose of 100 mg/m^2 in patients with good performance status and normal bilirubin levels. The dose should be reduced in patients with abnormal bilirubin levels.

The most common toxic effect in our study was fatigue, reported in 45 of 75 cycles in eligible patients receiving up to five cycles each. Although not severe, fatigue was a major cause of delayed treatment and occurred frequently after three cycles of chemotherapy. When required, treatment was discontinued for at least 1 week in patients with fatigue. This rest led to recovery in nearly all patients. Postponement of subsequent cycles of chemotherapy also promoted recovery from nausea and anorexia, two other common toxic effects. Neutropenia was another important reason for delaying treatment, and occurred in 42 of 75 cycles, including 7 with grade 3/4 neutropenia. Excluding the patient with DLT, neutropenia usually did not resolve after 1 week of rest. At the RD, the mean absolute DIs of 5-FU and irinotecan were 287 mg/m^2 per week and 62 mg/m^2 per week, and the relative DIs were 86% and 93%, respectively. Differences between the scheduled and administered doses were caused by temporary discontinuation of treatment and dose reduction. On the basis of our experience, we recommend that treatment be suspended for at least 1 week in patients with adverse events.

Our regimen was highly active, with a response rate of 69% in patients receiving the RD. Our overall response rate of 58% is similar to that in previous studies of irinotecan with 5-FU and LV. We conclude that combination of irinotecan, 5-FU, and *l*-LV is safe, effective, and clinically feasible, and this regimen could be one of the standard first-line treatments for metastatic colorectal cancer in Japan.

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ORIGINAL ARTICLE

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Gene expression of 5-fluorouracil metabolic enzymes in primary colorectal cancer and corresponding liver metastasis

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Abstract *Purpose*: Expression of thymidylate synthase (TS) and the 5-fluorouracil (5-FU) metabolic enzymes, including dihydropyrimidine dehydrogenase (DPD), orotate phosphoribosyl transferase (OPRT), thymidine phosphorylase (TP), and uridine phosphorylase (UP), has been reported to be associated with the sensitivity to 5-FU-based chemotherapy in colorectal cancer. We evaluated the correlation of the expression of these genes between primary tumors and corresponding liver metastases. *Method*: The mRNA levels of TS, DPD, OPRT, TP, and UP were measured by real-time quantitative RT-PCR in samples from 23 consecutive patients with both primary colorectal adenocarcinoma and liver metastasis. *Results*: The DPD, OPRT, TP, and UP mRNA levels were significantly higher in liver metastases than in primary tumor (expression in relation to that of β-actin mRNA: 0.42 vs 0.16, $P=0.00053$; 1.4 vs 0.92, $P=0.016$; 23 vs 11, $P=0.00014$; 0.36 vs 0.25, $P=0.0026$; respectively). However, the TS mRNA level did not differ significantly between liver metastases than primary tumor (0.20 vs 0.16, $P=0.28$). No correlation was observed for any gene between primary tumor and liver metastases. In both primary tumor and liver metastasis, the TS mRNA levels correlated significantly with the OPRT mRNA level (primary $r_S=0.83$, $P=0.00000081$; liver metastasis $r_S=0.49$, $P=0.017$), while the DPD mRNA level correlated significantly with the TP mRNA level $r_S=0.81$, $P=0.0000024$; $r_S=0.63$, $P=0.0014$; respectively). *Conclusions*: The differential gene expression of 5-FU metabolic enzymes between primary colorectal cancer and corresponding liver metastases should be taken into consideration when estimating the sensitivity to 5-FU-based chemotherapy in colorectal cancer. The gene expression of TS and OPRT, which are involved in de novo pyrimidine synthesis, and that of DPD and TP, may be coregulated.

Keywords Thymidylate synthase · Dihydropyrimidine dehydrogenase · Orotate phosphoribosyl transferase · Thymidine phosphorylase · Uridine phosphorylase

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Introduction

Thymidylate synthase (TS) protein and gene expression in human colorectal cancers has been investigated as a predictor of response to chemotherapies based on 5-fluorouracil (5-FU), and as a prognostic marker [1, 2, 5, 9, 10, 20, 24, 29]. Previous studies have suggested that high TS expression in advanced colorectal cancers, determined by several methods (immunohistochemical staining, enzyme activity, and reverse transcription PCR), is followed by non-response to 5-FU and poor prognosis.

The other 5-FU metabolic enzymes have been also examined as predictors of sensitivity to 5-FU. Dihydropyrimidine dehydrogenase (DPD) is the first and rate-limiting enzyme for the catabolism of 5-FU, and its activity or mRNA level is high in various human cancers and cell lines with low sensitivity to 5-FU [3, 11, 16, 19, 33]. Ichikawa et al. [17] and Salonga et al. [33] have reported that patients with both low DPD and low TS mRNA expression in primary colorectal cancers respond to 5-FU-based chemotherapy, and their prognosis is better than patients with both high DPD and high TS expression. Other studies have indicated that the expression levels of the first metabolic enzymes of 5-FU, namely orotate phosphoribosyl transferase (OPRT) [6, 18, 30, 31], thymidine phosphorylase (TP) [6, 12, 25, 27, 28, 33, 34], and uridine phosphorylase (UP) [6, 8, 18, 25, 35], might also correlate with sensitivity to 5-FU. High TP gene expression has been shown to be followed by low

Table 1 Primers and probes

	Forward primer	Reverse primer	Probe
TS	TS-1	TS-r3	TS-P2
	GAATCACATCGAGCCACTGAAA	CAGCCCAACCCCTAAAGACTGA	TTCAGCTTCAGCGAGAACCCAGA
DPD	DPD-F11	DPD-R11	DPD-P11
	AATGATTCGAAGAGCTTTTGAAGC	GTTCCCCGGATGATTCTGG	TGCCCTCACCAAAACTTTCTCTCTTGATAAGGA
OPRT	OPRT-1107F	OPRT-1282R	OPRT-1200PF
	TCCTGGGCAGATCTAGTAAATGC	TGCTCCTCAGCCATTCTAACC	CTCCTTATTGCGGAAATGAGCTCCACC
TP	TP-700F	TP-770R	TP-722P
	CCTGCGGACGGAATCCT	GCTGTGATGAGTGGCAGGCT	CAGCCAGAGATGTGACAGCCACCGT
UP	UP-586F	UP-792R	UP-743PF
	TGACTGCCCAGGTAGAGACTATCC	AGACCTATCCCACCAGAAGTGC	TGCTCCAACGTCACTATCATCCGCAT
β-ActinACTB	ACTB-517F	ACTB-811R	ACTB-547PF
	TCACCCACACTGTGCCCATCTACGA	CAGCGGAACCGCTCATTGCCAATGG	ATGCCCTCCCCCATGCCATCCTGCGT

chemosensitivity to 5-FU in colorectal carcinoma [33]. Chung et al. have reported that OPRT, TP, and UP gene expression is downregulated in gastric cell lines with 5-FU resistance [6]. These results indicate that multiple analysis of the expression of 5-FU metabolic genes may predict sensitivity to 5-FU more precisely.

However, the relationship between the expression of these genes in primary cancers and their expression at metastatic sites has not been adequately evaluated. We have previously shown that TS gene expression is lower, and DPD gene expression is higher, in liver metastases than in primary colorectal cancers [36, 39]. As high expression of TS, DPD and TP protein or mRNA has been reported to be associated with low sensitivity to 5-FU [2, 17, 20, 24, 33], the prediction of 5-FU chemosensitivity by analysis of expression in the primary tumor may be inaccurate in patients whose TS, DPD and TP gene expression is markedly higher or lower in their liver metastases than in the primary tumor.

In the present study, the expression of TS, DPD, OPRT, TP, and UP genes in primary colorectal cancer was compared with that in the corresponding liver metastases by real-time quantitative RT-PCR.

Materials and methods

Patients and samples

We analyzed pairs of primary colorectal adenocarcinomas and corresponding liver metastatic tumors from 23 patients (13 males and 10 females, average age 62.2 years) who had undergone surgical resection of primary colorectal cancer between October 1997 and October 2001 at the Department of Digestive Surgery, Tokyo Medical and Dental University, Tokyo, Japan. This study was approved by the Institutional Review Board of the Tokyo Medical and Dental University, and written consent was obtained from all patients. Of the liver metastasis samples, 12 were obtained by surgical resection, and 11 by intraoperative core-needle biopsy at the time of resection of the primary tumor. Seven were metachronous metastases and two of the patients had received 5'-deoxy-5-fluorouridine orally as adjuvant therapy after the primary resection. One of these two patients discontinued adjuvant therapy after only 4 weeks, while the other completed a 1-year course of adjuvant therapy. Resection of the liver metastases in this patient was performed at least 6 months after completion of the adjuvant therapy regimen.

Immediately following surgery, each tissue sample was frozen in liquid nitrogen and stored at −80°C until preparation of RNA extracts. A gastrointestinal pathologist evaluated the remaining specimens. No contamination of the normal colonic mucosa or liver tissue in the tumor samples was histologically identified.

Total RNA extraction and cDNA synthesis

Our procedure has previously been described in detail [36, 38, 39]. In brief, total RNA was extracted using an RNeasy Minikit (Qiagen, Chatsworth, Calif.). The amount of total RNA was estimated by measuring absorbance, the quality was determined by electrophoresis through agarose gel in the presence of formaldehyde, and the rRNA bands were visualized. Then up to

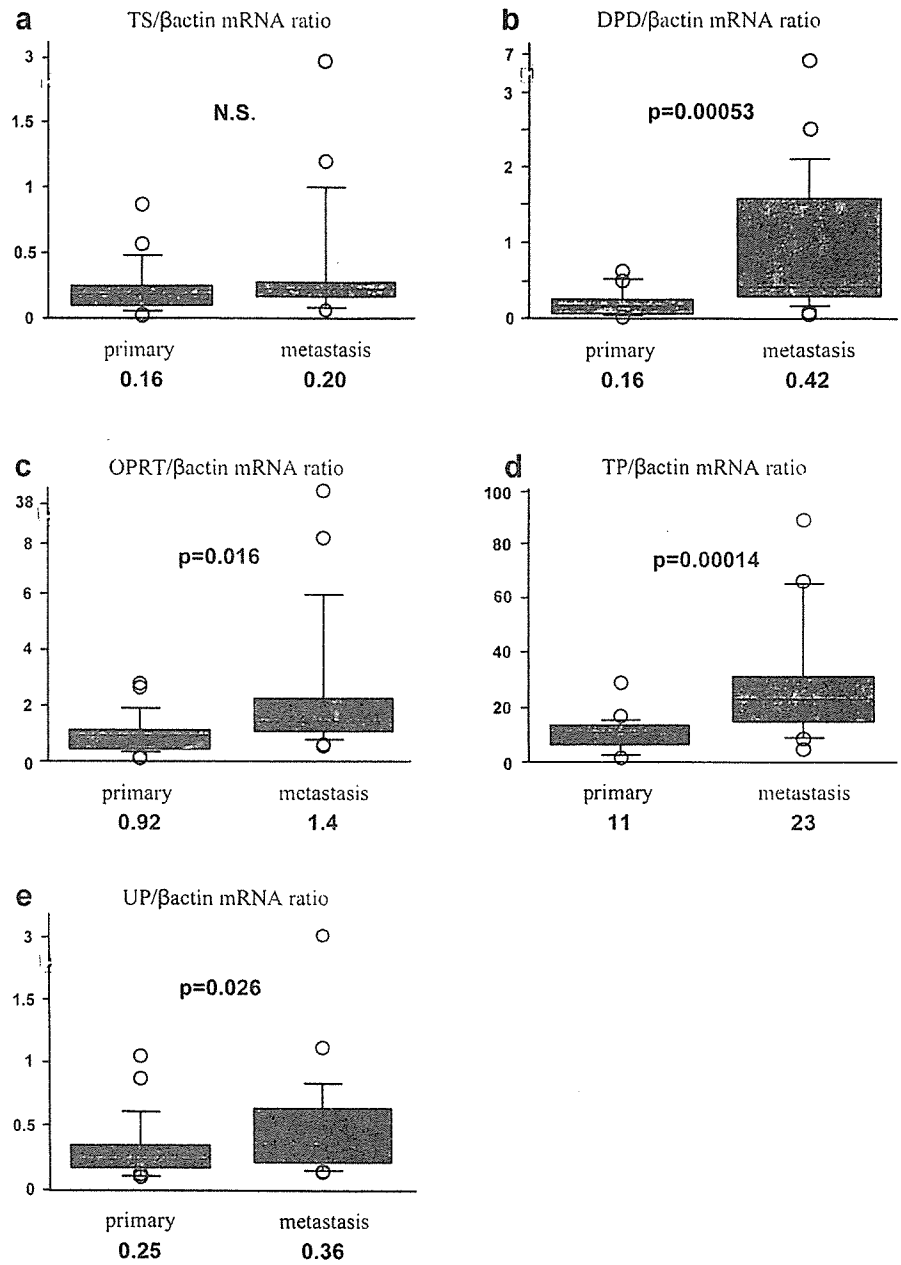

Fig. 1a–e Gene expression in primary tumors and liver metastases. The median values are shown

10 μg of the prepared RNA was reverse-transcribed to synthesize cDNA using the oligo(dT) primer, Superscript II (Life Technologies, Gaithersburg, Md.), as previously described.

Real-time quantitative RT-PCR assay

The mRNA levels of TS, DPD, OPRT, TP, and UP were evaluated by real-time quantitative RT-PCR [15, 29, 30] (TaqMan PCR) using an ABI Prism 7700 sequence detector (Perkin-Elmer Applied Biosystems, Foster City, Calif.). The β-actin gene was used as the endogenous control gene. Primers and TaqMan probes for each gene were designed based on the nucleotide sequence of human TS, DPD, OPRT, TP, UP and β-actin (Table 1). The PCR mixture contained 10 μl of each appropriately diluted cDNA sample (standard curve points and patient samples), 200 n*M* forward primer, 200 n*M* reverse primer, 100 n*M* TaqMan probe, and 12.5 μl TaqMan Universal PCR Master Mix (Perkin-Elmer Applied Biosystems), in a final volume of 25 μl. The PCR profile consisted of one incubation at 50°C for 2 min, one incubation at 95°C for 10 min, and 45 cycles of amplification for 15 s at 95°C, and 1 min at 60°C.

The amount of PCR product was determined using a standard curve of cDNA synthesized from human tumor xenograft. Each PCR run included the seven points of the standard curve (fourfold serially diluted cDNA with 100 ng/μl) and negative controls. The range of the standards was 64 to 0.00391 ng/10 μl. All samples were run in duplicate PCR experiments. The mean was then used; a few samples with more than a twofold difference in the amount of PCR product were retested. Some samples out of the range of the respective points on the standard curve were also retested using altered cDNA concentrations.

The relative amount of each gene's mRNA was expressed as the ratio of each mRNA to that of β-actin.

Statistical analysis

The mRNA levels and clinicopathological factors were compared using the Mann-Whitney *U*-test. The mRNA levels of the primary colorectal cancers and those of the liver metastases were compared

using the Wilcoxon signed-ranks test. The relationship between each gene's mRNA level in the primary cancer and that in the liver metastases, and the relationships among the mRNA levels in primary cancers or liver metastases were assessed using Spearman's rank correlation. Statistical significance was established at the $P < 0.05$ level for each analysis.

Results

Messenger RNA levels of the 5-FU metabolic enzymes were assessed in 23 pairs of primary colorectal cancers and corresponding liver metastases. The difference in the quantities between duplicate PCR products was less than 10%. No significant differences in mRNA levels were observed for any clinicopathological features such as gender, age, location of primary tumor, number of liver metastases and method of obtaining samples from liver metastases. Synchronous and metachronous liver metastasis showed the same levels of gene expressions (median values: TS 0.20 vs 0.22, $P=0.69$; DPD 0.57 vs 0.42, $P=0.64$; OPRT 1.6 vs 1.4, $P=0.64$; TP 26 vs 21, $P=0.42$; UP 0.44 vs 0.32, $P=0.74$).

DPD, OPRT, TP and UP mRNA levels in the liver metastases were significantly higher than those in the corresponding primary tumors (DPD 0.42 vs 0.16, $P=0.00053$; OPRT 1.4 vs 0.92, $P=0.016$; TP 23 vs 11, $P=0.00014$; UP 0.36 vs 0.25, $P=0.026$; Fig. 1). The TS mRNA level did not significantly differ between the liver metastases and the primary tumors (0.20 vs 0.16, $P=0.28$). No significant correlation between the mRNA levels of the primary tumors and those of their corresponding liver metastases was noted for any of the genes (TS $P=0.48$, DPD $P=0.94$, OPRT $P=0.19$, TP $P=0.81$, UP $P=0.90$). There was a significant correlation between the OPRT and TS mRNA levels both in the primary tumors ($r_S=0.83$, $P=0.00000081$; Fig. 2a) and in the liver metastases ($r_S=0.49$, $P=0.017$; Fig. 2b). A similar relationship was noted between DPD and TP mRNA levels in both primary tumors ($r_S=0.81$, $P=0.0000024$; Fig. 3a) and liver metastases ($r_S=0.63$, $P=0.0014$; Fig. 3b). Other correlations among the genes were not found.

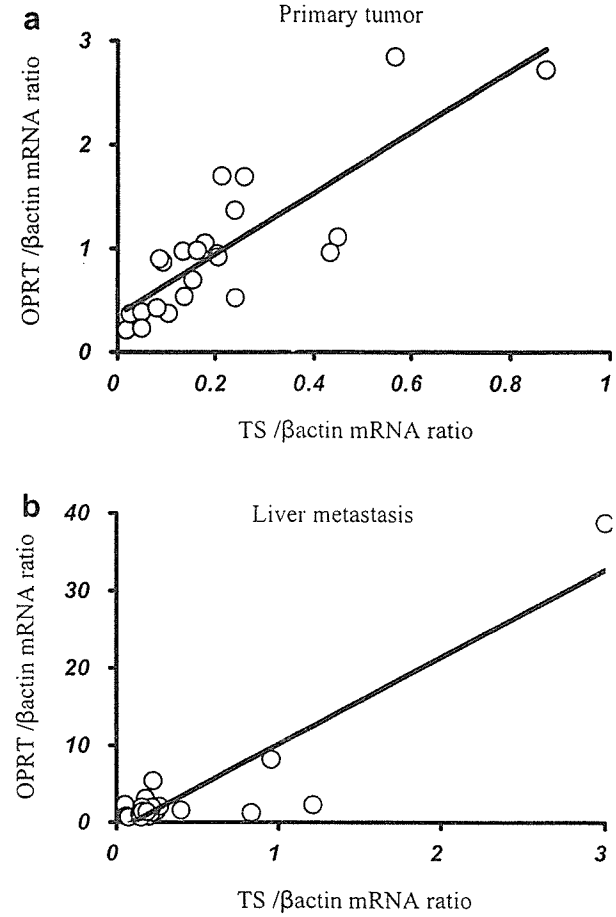

Fig. 2a, b TS and OPRT mRNA levels are significantly correlated in both primary colorectal cancers (**a** $r_S=0.83$, $P=0.00000081$) and liver metastases (**b** $r_S=0.49$, $P=0.0017$)

Discussion

We demonstrated that DPD, OPRT, TP, and UP mRNA levels in liver metastases were significantly higher than in their corresponding primary colorectal cancers, although no correlation was observed between primary tumors and liver metastases. Previously, we have shown that DPD gene expression in colorectal cancers is associated with tumor progression, and that higher DPD gene expression is present in liver metastases than in primary tumors [36]. Johnston et al. have suggested that suppression of translation of DPD mRNA is removed in tumor tissue, and proposed a general mechanism by which pyrimidine nucleotide biosynthesis and degradation are coregulated to maintain a growth advantage in the tumor [21]. Takebayashi et al. have reported that TP, which catalyses the reversible phosphorolysis of thymidine and its analogues to their respective bases 2-deoxyribose-1-phosphate, is associated with tumor progression [37]. Previous investigators have shown that the expression of the initial 5-FU-anabolizing enzymes (OPRT, UP, TP, etc.) is higher in various human cancers than in normal tissues [7, 22, 26, 32], and suggested that the increase in the expression of these enzymes may be an advantage via increased pyrimidine nucleotide biosynthesis for cell proliferation in cancer. The gene expression of thymidine kinase (TK), one of the enzymes involved in salvage DNA synthesis, correlates with malignant potential in ovarian tumors, as well as with TP gene expression [13].

In the present study, a linear relationship between TS and OPRT mRNA levels was observed in both primary colorectal cancers and liver metastases. Kasahara et al. have reported that TS gene expression correlates closely with E2F1 expression, and speculated that one mechanism by which tumor cells increase TS expression may be overexpression of E2F1, which induces S-phase-acting proteins such as TS [23]. Fujiwaki et al. have

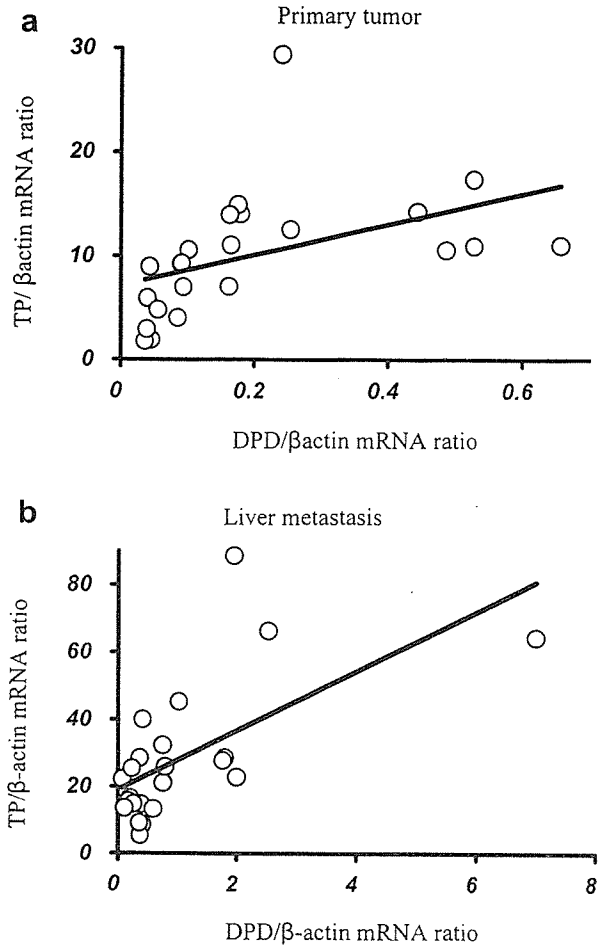

Fig. 3a, b DPD and TP mRNA levels are significantly correlated in both primary colorectal cancers (**a** $r_S = 0.81$, $P = 0.0000024$) and liver metastases (**b** $r_S = 0.63$, $P = 0.014$)

demonstrated a linear relationship in gene expression levels between TK1 and TS in ovarian cancer, suggesting that enzymes for DNA biosynthesis may be controlled by several similar mechanisms [13]. TS and OPRT, which are involved in de novo pyrimidine nucleotide biosynthesis, may be coregulated in cancer cell proliferation. DPD and TP gene expression were also positively correlated in both primary cancers and liver metastases. Collie-Duguid et al. suggested that the expression of DPD and TP protein is coregulated [7].

We measured gene expression using the TaqMan RT-PCR assay. This method is a more precise and reproducible semiquantitation of gene expression than conventional RT-PCR assays using agarose gel, because it is based on threshold values in the exponential phase of the PCR rather than end-point measurement of the amount of PCR product [4]. In addition, this PCR assay is suitable for smaller samples such as biopsy specimens and can measure a larger number of enzymes in a shorter time than other methods, including enzymatic activity or protein assays [24].

Increased OPRT gene expression in liver metastases may be associated with increased sensitivity to 5-FU, because OPRT is a 5-FU-anabolizing enzyme and is considered the main pathway of 5-FU initial phosphorylation in human cancers [14]. On the other hand, increased TS, DPD, and TP may be associated with decreased sensitivity to 5-FU. In patients with extremely low expression of OPRT mRNA or high levels of TS, DPD, or TP gene expression in liver metastasis, it may be difficult to predict 5-FU sensitivity of the metastasis via analysis of the gene expression of the primary site.

The present study showed that the expression of 5-FU metabolic genes in liver metastases does not correlate with that in the corresponding primary tumor. The difference in the expression of 5-FU metabolic genes between the primary site and liver metastases should be taken into consideration when predicting the sensitivity to 5-FU-based chemotherapy of colorectal cancer.

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特集／大腸・肛門疾患 — 最新の診断と治療

転移性大腸癌の診断と治療

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はじめに

近年，高齢化や食生活の欧米化に伴い大腸癌は増加している。大腸癌は分化度が高く比較的限局性に発育し，また系統的なリンパ節転移をきたすので，腹腔内の膜構造をよく把握した系統的な手術を行えば外科的治療の有効性が高い癌である。stage Ⅱ症例の20%弱（結腸癌15%，直腸癌20%），stage Ⅲ症例の約30%（同25%，35%）が再発する[1)-3)]。再発部位は肝，肺，骨の順に頻度が高く，直腸癌では約10%が骨盤内再発をきたす。切除可能な肝，肺，骨盤内再発に対しては外科治療が第一選択となり，切除不能転移・再発病巣に対する治療の第一選択は化学療法である。古典的なレジメンの化学療法の奏効率は20%程度，新規薬剤を用いた多剤併用療法では30～40%である。本稿では，転移・再発症例に対する手術療法，全身化学療法や肝動注療法（肝動注），加えて転移・再発の予防＝術後補助化学療法の現況と，将来の展望を概説する。

Ⅰ．外科治療

切除可能な肝，肺転移や骨盤内再発に対しては外科治療が第一選択である。

1. 肝転移

肝臓は大腸癌の転移が最も高頻度に起こる臓器である。肝切除の適応となる症例は欧米で25%程度，我が国では40～50%である。この相違は，フォローアップスケジュールや切除の適応の差異によるものと思われる。肝切除後の5年生存率は30～50%である。残肝再発率は50～60%で，20%は肺など肝外転移をきたすと報告されている。

2. 肺転移

肝転移が大腸癌切除後比較的早期（1～2年）に発見されるのに対し，肺転移は術後2年以降の再発が約半数である。肺転移の頻度は6～7%であり，そのうち切除の適応となる症例は10～30%に過ぎない。しかし肺転移治癒切除後の5年生存率は30%程度で肝切除とほぼ同等であり，手術適応のある症例に対しては積極的に肺切除が行われている[1)4)]。

3. 骨盤内再発

直腸癌症例の約25%が骨盤内再発をきたす。このうち約半数は骨盤外病変を伴わないので，近年は骨盤内臓全摘術や仙骨合併切除などの拡大手術が行われている。治癒切除例の5年生存率は，20～30%である。また化学放射線療法と手術療法を併用することにより，予後の改善が試みられている。

Ⅱ．切除不能転移・再発巣に対する治療

切除不能転移・再発巣に対する治療の主体は化学療法である。肝転移に対する治療のオプションとしてはmicrowave coagulation therapyやradiofrequency ablation，免疫療法などもある。当科における治療方針を表1に示した。直腸癌骨盤内再発に対しては，化学放射線療法を行っている。

化学療法は，1）薬剤投与経路，2）使用する薬剤，3）投与時間の3つの要素により分類可能である。現時点でわが国で行われている化学療法に関しては，1）としては肝動注化学療法（以下肝動注）と全身投与，2）としては5-FU系薬剤＋活性型葉酸（LV，*l*-LV）とCPT-11，3）としては急速静(動)注と持続静(動)注となる。現在，5-FU系薬剤および葉酸製剤は，内服薬を使用するレジメンが注目されている。当科ではUFT＋LV(経口)＋CPT-11療法のPhase Ⅰ/Ⅱ Studyを行っている（表1）。

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表　1　当科における切除不能・再発大腸癌の治療方針

再発部位	First line	Second line	Third line 以降
直腸癌局所再発 (切除不能例)	化学放射線治療 UFT＋LV 5投2休，25日間 照射50Gy	⇒ UFT＋LV(経口) ＋CPT-11	⇒ 5-FU＋*l*-LV
肝転移単独 (切除不能例)	肝動注化学療法 5-FU 1,250 or 1,500mg週1回 *l*-LV 静注を加えることあり	⇒ UFT＋LV(経口) ＋CPT-11	⇒ 5-FU＋*l*-LV
その他の切除不能症例	経口摂取可 UFT＋LV(経口)＋CPT-11	⇒ 5-FU＋*l*-LV または S-1	
	経口摂取不可 5-FU＋*l*-LV	⇒ CPT-11	

表　2

	primary tumor	liver metastasis
TS median (range)	0.17 (0.019～0.87)	0.21 (0.052～3.0) NS
DPD	0.16 (0.036～0.66)	0.51 (0.073～7.0) p＝0.0007
OPRT	0.94 (0.21～2.8)	1.5 (0.63～39) p＝0.022
TP	11 (1.8～29)	23 (5.4～89) p＝0.0002
UP	0.24 (0.090～1.0)	0.38 (0.14～3.0) p＝0.0099

1. 肝動注化学療法

1）理論的背景

切除不能肝転移に対して肝動注を行う理論的根拠は以下の2つである。①肝転移巣は主に肝動脈から血流を受けるが正常肝細胞は門脈から受けている。従って，肝動注により肝転移巣は高濃度の薬剤と接触するが，正常肝細胞に対する障害は少ない。②肝動注に使用される5-FUは大部分が肝で速やかに代謝されるため，全身的副作用は比較的軽微である。

2）適　　応

切除不能な肝転移で肝外病変がなく，主要な臓器機能が保たれている症例が適応となる。また肝外病変があっても肝転移が生命予後を決定すると判断される症例に対しては，相対的適応として肝動注が行われる。

3）レジメン

わが国では間欠的大量5-FUの5時間注入(Weekly high-dose infusion＝WHI)が好んで行われている。当科においては，WHIに*l*-LV静注を付加することにより治療効果の上乗せが見られるかを検証する多施設共同第3相臨床試験を進行中である（表1）。また5-FUの感受性因子であるTS(thymidylate synthase，5-FUの標的酵素)，DPD（dihydropyrimidine dehydrogenase，5-FUの代謝律速酵素）およびOPRT（orotate phosphoribosyl transferase，5-FUの活性化酵素）のmRNAの大腸癌肝転移巣における発現量をRT-PCR法にて定量した研究[5]では，原発巣に比し肝転移巣では，TS mRNA量は同等，DPDおよびOPRT mRNA量は高いことを示した（表2）。加えて正常肝細胞のDPD mRNAレベルは肝転移巣よりもさらに3.8倍高かった[6]。この結果からWHIにより少ない副作用で高い奏効率が得られることが論理的に裏付けられた。すなわち肝転移巣における高い5-FU分解能に対し，それに打ち勝つ高濃度の5-FUを接触させることができ，またTSやOPRT mRNAレベルからは潜在的に5-FUの感受性があると考えられる肝転移巣に対して，抗腫瘍効果が得られる。また正常肝では高濃度の5-FUを分解する能力が十分にある，と予測される。

5-FUのWHIのほか，CDDPやMMC，IL-2などを5-FUと併用して肝動注するレジメンもある。

4）治療効果

肝動注の奏効率は高く，42～62%と報告されている。荒井らの報告ではCR 23%，奏効率は83%に及ぶ[7]。しかし，肝動注と全身化療のランダム化試験では，肝動注は全身化療に比べて生存期間の延長に貢献することが立証されていない。メタアナリシスによる解析でも，生存期間の延長は明らかにされなかった。その理由は，肝動注では肝外病変のコントロールが不十分となるからである。また，市川らは解析における「cross over」症例，

表　3　5-FU＋LV の代表的投与レジメン

Mayo レジメン	5-FU 静注(370mg/m²)＋LV 低用量(20mg/m²)静注，5日間連続，4週毎繰り返し
Roswell Park レジメン	LV 高用量(500mg/m²) 2時間で点滴静注，1時間経過後 5-FU 静注(500mg/m²，後に推奨用量は600mg/m²となった)，週1回，計6回投与
de Gramont レジメン	LV 高用量(200mg/m²)静注(2時間)→5-FU 静注(400mg/m²)→5-FU 持続点滴(600mg/m²/22時間)，2日間連続，2週毎投与

すなわち全身化療後に肝動注に移行する症例の影響を指摘している。わが国では荒井らの報告などにより，リザーバー留置技術や肝への確実な薬剤分布の確認など技術面の重要性が認識され，欧米に比し精密な肝動注療法が行われているので，前述の *l*-LV 付加による治療効果の上乗せの検証も含め，肝動注療法の予後への寄与が検討されるべきである。

2. 全身化学療法

1）5-FU 系薬剤＋LV

5-fluorouracil (5-FU) の開発以来40年を経ているが，5-FU 系薬剤は現在も大腸癌化学療法の中心的存在である。その作用機序は，①5-FU の代謝産物である F-dUMP と還元型葉酸，そして *de novo* DNA 合成酵素である Thymidylate synthase (TS) が三者共有結合体を形成することにより，DNA 合成が阻害される。②5-FU が核酸に取り込まれ (F-DNA，F-RNA) 核酸に機能障害をきたすことである。現時点でエビデンスの確立した全身化療は，5-FU+LV である。5-FU の作用を増強するための葉酸の有効な血中濃度は1 μM～10μM23)，とされているが，臨床的な投与量・投与法についてはさまざまなレジメンで検討されている。代表的な投与レジメンを表3に示した。奏効率は当初30～40%とされていたが，最近では20～30%弱と報告されている。現在我が国で保険適応のある 5-FU+LV の点滴静注法は，Roswell Park レジメン(表3)に準じた 5-FU 600mg/m² 静注＋*l*-LV 250mg/m² 2時間点滴静注である。一方，利便性を考慮して 5-FU 系薬剤と LV の一方あるいは双方を経口投与する方法が注目されている。我々は進行・再発大腸癌患者に対し，利便性と外来治療を目指し UFT-E® 400mg/m²/日＋経口 LV 15mg/日を5日間連続投与後2日休薬，4週間投与を1クールとするレジメンにより，12/37＝32.4%の奏効率を得ている[8]。また日米の bridging study などでも，UFT＋経口 LV 療法は 5-FU＋静注 LV と同等の治療効果を持つことが示されつつある。UFT＋経口 LV 療法は進行再発大腸癌に対する標準治療の一つとなると考えられる。

2）CPT-11

CPT-11はトポイソメラーゼⅠ阻害により抗腫瘍効果を発揮し，5-FU と交叉耐性を示さない薬剤である。単独投与でも大腸癌に対して約25%の奏効率が示された。またこれらの Phase Ⅱ study は5-FU 抵抗性大腸癌に対する CPT-11の有効性を示しており，second line の標準治療として確立された。

最近は，5-FU 系薬剤＋LV に CPT-11を付加するレジメンに関する検討が広く行われている。Saltz[9]らおよび Douillard[10]らは，5-FU＋LV あるいは CPT-11単剤投与に比し 5-FU＋LV＋CPT-11療法は奏効率，time to progression (TTP) および生存期間において優れていると報告した。我々は従来の UFT-E® 400mg/m²/日＋経口 LV 15mg/日（上述）の第1および第15日に CPT-11を点滴静注するレジメンの Phase Ⅰ/Ⅱ Study を進行中であり（表1）現在のところ奏効率は40%前後である。また，de Gramont レジメン（表3）に準じた 5-FU＋LV 療法と CPT-11や Oxaliplatin（我が国では未承認，後述）を併用投与する FOLFIRI あるいは FOLFOX 療法も高い奏効率を示すと欧米で報告され，我が国でも追試されている。この治療法では静注リザーバー埋め込みが必要となる。

3）そ　の　他

CPT-11と同様にわが国で開発され，欧州で臨床使用が開始された Oxaliplatin の有効性も注目されている。わが国では同じプラチナ製剤として CDDP を用い，5-FU との併用療法が行われてきたが，大腸癌に対して CDDP は保険適応外である。Oxaliplatin と 5-FU の併用投与の有効性，有害事象に関しては今後の検討課題である。

Capecitabine は 5-DFUR の pro-drug である。

Twelvesらは進行再発癌に対し，Capecitabine単剤投与によって25.7%の奏効率を得た。生存期間も5-FU+LVと同様であったと報告している。

Ⅲ．転移の予防；術後補助化学療法

海外では5-FU系薬剤とLVやlevamisole(LEV)を組み合わせたレジメンで数々の大規模比較試験が行われ，わが国では梶谷班一次研究以降5-FU系薬剤とMMCの併用投与を中心に行われた。現在は進行再発癌に対するレジメンと同様に5-FU系薬剤+LV（経口剤を含め）の有用性が示されつつある。投与期間は6ヵ月が標準とされる。

治癒切除後補助化学療法を行う対象　米国National Cancer Institute（NCI）がインターネット上に公開している推奨治療によると，StageⅢ結腸およびStageⅡ・Ⅲ直腸癌に術後補助化学療法(直腸癌には放射線治療も選択肢となる）が施行されるべきであるとしている。StageⅡ大腸癌に対する補助化学療法は意見の分かれるところであるが，StageⅢ（Dukes C）症例においては補助化学療法の有効性が認知されている。わが国ではmeta-analysisにより，StageⅢ大腸癌において経口5-FU-based regimenは手術単独群と比較して再発率および死亡率を有意に減少させたと報告された。

レジメン　National Surgical Adjuvant Breast and Bowel Project（NSABP）は代表的な大規模比較試験である。1987年から行われたNSABP C-03から5-FU+LVの検証がなされた。またStageⅢ症例に対する術後補助化学療法の有効性が明らかになりつつあったので，臨床試験において手術単独群をおくことが問題となり，C-03からは対照群としての手術単独群はおかれていない。NSABPにより補助化学療法としての5-FU+LVの有用性が示された。C-06ではUFT+経口LVが5-FU+LVと同等の効果であることが示され，C-07においてはOxaliplatinと5-FU+LVとの併用投与の有用性について検討中である。

大腸癌術後再発予防を目的とした門注療法，および肝切除後の再々発予防を目的とした肝動注療法の効果については議論のあるところである。全身投与の補助化学療法レジメンと比しsurvival benefitを認めないとされることも多く，上述のNCIによる推奨治療において術後補助門注療法は“is therefore of some historical interest and should not be employed”と位置付けられている。

Ⅳ．今　後　の　展　望

標準的全身化療は5-FU+LVであるが，わが国でも使用可能となった経口剤（UFT+LV）の使用やCPT-11との併用投与法などについて臨床試験がすすんでいる。またOxaliplatinやS-1，Capecitabineなどの新規抗癌剤も大腸癌に対して効果が期待できる。肝動注に関しては，今後は全身化療やLVとの併用で予後改善への寄与を検討する必要がある。米国ではFUDRの肝動注とCPT-11全身投与の併用試験が開始され，注目されている。

近年，腫瘍の個性に応じて個別化された化学療法を行う試み（オーダーメイド治療）が盛んに論じられている。TSやDPD，OPRTの他にも抗癌剤に対するマーカーが発見され，プロスペクティブな検討で効果予測の有用性が示されれば，大腸癌化学療法におけるオーダーメイド治療の確立の一助となるであろう。

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ORIGINAL ARTICLE

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Results of surgical treatment for multiple (≥5 nodules) bi-lobar hepatic metastases from colorectal cancer

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Abstract *Background:* The surgery for the treatment of multiple (≥5) bi-lobar hepatic metastases from colorectal cancer is controversial. This retrospective study presents our experience in an attempt to develop reasonable treatment guidelines. *Method:* One hundred sixty-one consecutive patients who underwent liver resection with curative intent were classified into three groups: H1 (unilateral), H2 (bilateral, ≤4 nodules), or H3 (bilateral, ≥5 nodules). *Results:* The overall cumulative 5-year survival rate was 46.7%. Survival was similar among patients with H1, H2, and H3 disease. Thirty-two patients with H3 disease underwent hepatectomy: straightforward hepatectomy in 12, portal vein embolization (PVE) prior to hepatectomy in eight, two-stage hepatectomy in two, and two-stage hepatectomy combined with PVE in ten. Two-stage hepatectomy with or without PVE was the standard approach in patients with synchronous liver metastases. The operating mortality in hepatectomy for H3 disease was 0%, and the morbidity was 15.2%. The overall response rate to neoadjuvant chemotherapy (NAC) was 41.7% (5/12). Patients who responded to NAC (n=5) had a better prognosis than non-responders (n=7) (P<0.05). *Conclusions:* Extended hepatectomy, including preoperative PVE and multi-step hepatectomy, combined with NAC, may result in a favourable prognosis, especially in patients who respond to NAC, but further studies with more patients are needed to confirm this.

Keywords Colorectal cancer · Multiple hepatic metastases · Bi-lobar hepatic metastases · Neoadjuvant chemotherapy · Hepatectomy

Introduction

Surgical resection is still the gold standard treatment for patients with liver metastases from colorectal cancer, with 5-year survival rates of 30 to 40%. However, the hepatectomy rate in the patients is only 25% [1, 2]. At the beginning of hepatic surgery for colorectal metastases, only small, solitary, uni-lobar, lesions were resected. With progress in surgical techniques and improved surgical skill, the indications for hepatectomy were extended to include larger tumours, multiple unilateral metastases and eventually, to multiple bi-lobar metastases when they could be removed entirely [1, 2]. Some patients who suffer recurrence after liver resection can undergo repeat resection with benefit similar to that of the original procedure [3, 4].

It is true that new techniques, such as preoperative portal vein embolization (PVE), ultrasound-guided hepatectomy, and multi-stage hepatectomy, have made extended hepatic resection safer. However, the survival benefit of extended resection, combined with preoperative chemotherapy for bilateral multiple metastases, has not been established.

This paper reports our experience in treating multiple bi-lobar liver metastases from colorectal cancer.

Patients and methods

Patients

Between 1992 and 2001, 277 patients who were diagnosed as having liver metastasis from colorectal cancer were referred to the Department of Surgery II, Yokohama City University. Among these patients, 163 underwent liver resection with curative intent. Resection was incomplete in two patients. Consequentially, 161 patients (58.1%) of all patients with hepatic metastasis underwent potentially curative resection.

We classified liver metastasis according to the Japanese general rules for colorectal cancer [5] as follows: H1, liver tumours confined to one major lobe; H2, ≤4 hepatic tumours in both lobes; and H3, ≥5 bi-lobar hepatic tumours.

Computed tomography (CT) scans of the thorax, abdomen and pelvis, as well as abdominopelvic ultrasonography, were performed before hepatectomy to stage liver and extra-hepatic disease. CT arterioportography or SPIO MRI were also performed so as to confirm the exact number of liver tumours.

Surgical management

Hepatic resection was attempted in patients with hepatic metastases where the potential for cure was high and the patient was likely to tolerate the procedure, regardless of the number of hepatic lesions. Concurrent pulmonary metastases were not a contraindication because these lesions do not significantly affect survival after hepatectomy for liver metastases [6]. However, straightforward hepatic resection was not performed in patients with uncontrollable primary recurrence, diffuse peritoneal dissemination, advanced stage of lymph node metastases, or other extra-hepatic distant metastases. Hepatectomy may or may not have conformed to the principles of anatomic resection. A hepatectomy that ensured tumour-free margins was the guiding principle.

Intraoperative hepatic ultrasound was used routinely to examine the margin of the tumour and to detect the presence of occult metastatic lesions. Lesions were resected with a CUSA system, with isolation and division of hilar inflow and hepatic vein outflow after parenchymal transection in cases of lobar resection.

When a few small nodules remained after major hepatectomy, or when resection was contraindicated even by a two-stage procedure or with preoperative PVE, adjunctive microwave tissue coagulation therapy (MCT) using the model HS-15 M (Nippon Koden, Japan) was performed in otherwise unresectable cases to allow complete treatment of tumours. The decision to use MCT was made on a case-by-case basis according to the intraoperative findings.

Preoperative PVE and multi-stage hepatectomy

Even when the tumour was technically resectable, resection was still contraindicated if the anticipated size of the remnant liver was so small that severe postoperative liver failure was a risk. PVE of the liver has been developed as a technique to induce contralateral compensatory hypertrophy of the future remnant liver, followed by hepatectomy after an interval of 3 weeks. Straightforward hepatectomy was indicated in patients with a prognostic score [7] of less than 50, calculated from the indocyanine-green retention test, expected liver resection volume by CT volumetric analysis [8], and age. Mapping, using CT with arterioportography (CTAP), permits the surgeon to resect the greatest number of tumours, with the potential for additional resection of any remaining tumours after regeneration. If a right hepatectomy or a more extended hepatectomy were required to remove synchronous metastases, hepatic resection was not performed concurrently with the colorectal resection. It was our practice to carry out the hepatectomy at least 2

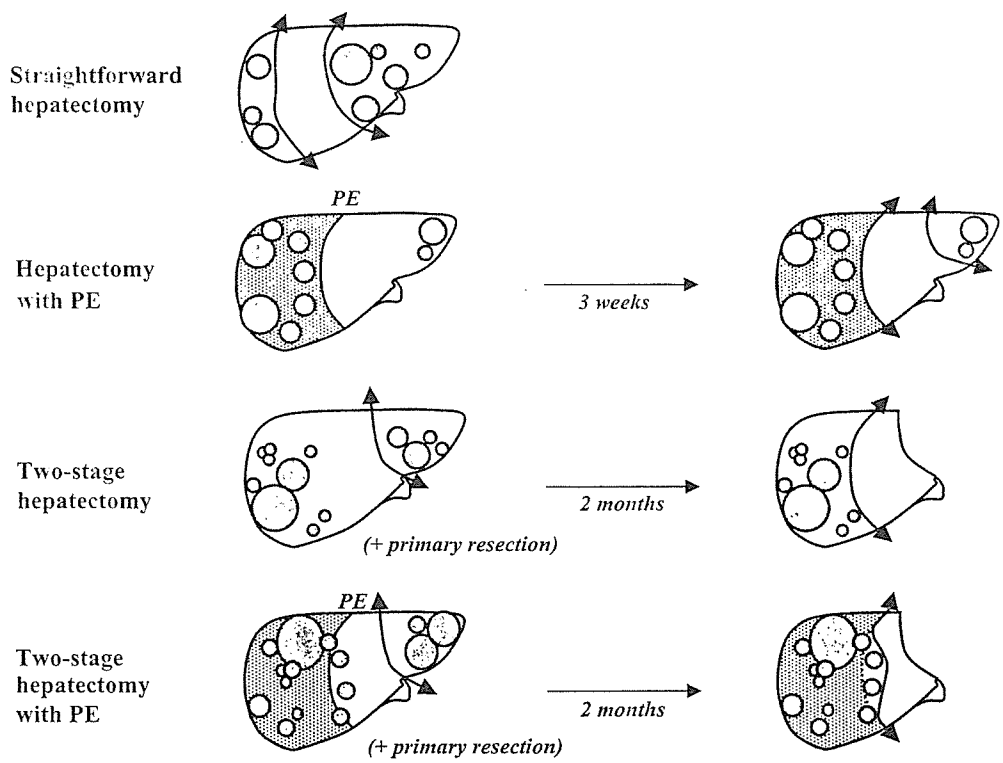

Fig. 1 Treatment strategies for multiple (≥5) bi-lobar liver metastases from colorectal cancer. *Grey area* shows embolized liver lesion. *Curved arrows* are lines of resection. *PE* portal vein embolization

months after resection of the primary when more than a small part of liver needed to be removed. Percentage of future liver remnant to whole liver volume was arbitrarily considered to increase by approximately 10% after PVE, based on previous work [9]. Therefore, when the anticipated liver remnant weight after PVE would be less than 25% of the total volume, the minimum volume needed for a safe resection [10, 11], a two-stage hepatectomy with PVE was performed. The timing of the second hepatectomy was a function of liver regeneration, and the likelihood that the second hepatectomy would be curative was based on the condition of the remnant liver tumour. The median interval between the two hepatectomies was 2 months (Fig. 1).

Neoadjuvant chemotherapy for patients with H3 disease

Neoadjuvant chemotherapy (NAC), or chemotherapy before hepatectomy or before the major hepatectomy in a two-stage hepatectomy, was administered to 12 of the 32 patients who underwent resection for H3 disease.

These neoadjuvant chemotherapy regimens were conducted regardless of initial resectability. However, in almost all cases in which neoadjuvant chemotherapy was given, it was initially considered to be difficult to remove all the liver tumours present with straightforward hepatectomy.

NAC was administered via the hepatic artery. The protocol consisted of a 5-day course of NAC, days 1 to 5 cisplatin (CDDP) (10 mg/day), l-folinic acid (FA) (150 mg/day) and 5-fluorouracil (5-FU) (500 mg/day), which was repeated at 14-day intervals, with a 9-day interval of recovery. 5-FU and FA were infused continuously, and CDDP was injected as a bolus. Four cycles were administered. The response to NAC was assessed after the four courses and defined according to the following criteria: (1) complete response (CR), complete disappearance of all symptoms and signs of disease for a minimum of 9 weeks; (2) partial response (PR), a 50% reduction (or more) in the sum of the products of the perpendicular diameters of measurable disease and the appearance of no new malignant lesion for a minimum of 9 weeks; (3) minor response (MR), a 25% or greater reduction but less than a 50% decrease in the size of sentinel lesions; (4) stable disease (SD), appearance of no new lesions, less than 25% decrease or less than 25% increase in the size of measurable lesions; and (5) progression disease (PD), more than 25% increase in the size of measurable lesions and/or the appearance of new lesions. CR or PR was considered to be indicative of effective or responsive treatment for the purpose of data analysis.

Patient follow-up

After being discharged, patients received adjuvant chemotherapy via the hepatic artery with 5-FU (1,500 mg/over 24 h) once a week for 8 weeks. For data analysis, the patients were classified into two groups: those whose total administered dose of 5-FU was <5,000 mg and those whose total administered dose of 5-FU was ≥5,000 mg.

Patients were followed-up at our outpatient clinic monthly. Data were abstracted from each patient's clinical record, and long-term outcome was obtained through clinical follow-up, tumour registry follow-up, and contact with the patient, family, or referring physician when necessary. No patients were lost to follow-up. The serum carcinoembryonic antigen (CEA) concentration was measured every month, a CT scan was performed every 3 months, and a chest roentgenogram was obtained every 6 months for 5 years after the last surgery.

The cumulative survival rate was calculated by the Kaplan–Meier method. The significance of differences in the survival curves was determined by the log-rank test. Statistical comparisons of baseline data were performed by Student's t-test or the χ^2 test. The level of significance was defined as $P<0.05$.

Results

Resection rate

The overall resection rate was 58.1% (161/277). According to the extent of liver metastases, 90.3% (93/103) of patients with H1, 72.0% (36/50) of patients with H2, and 25.8% (32/124) of patients with H3 disease underwent resection. The reasons why resection was not attempted in patients with H3 disease included unfeasibility of curative hepatectomy (42.4%), unresectable primary lesion (16.3%), extra-hepatic metastases (23.9%), local recurrence (5.4%), poor general condition (5.4%), and refusal of treatment (6.5%). The mortality rate was 0.6% (1/161).

Survival after hepatectomy

The median follow-up period for the 161 patients who underwent hepatectomy was 36.2 months (range 1 to 134 months). Overall cumulative survival was 88.3% for 1 year, 59.1% for 3 years, and 46.7% for 5 years after surgery. The cumulative 5-year survival rates for patients with H1, H2, and H3 disease were 51.2%, 42.8%, and 40.2%, respectively. Survival in the three groups was similar ($P=0.072$) (Fig. 2). Cumulative liver recurrence-free rates were 73.4% for 1 year, 52.4% for 3 years, and 49.7% for 5 years after surgery. The remnant liver recurrence-free rates 5 years after hepatectomy were 59.3%, 38.5%, and 29.5%, respectively. The remnant liver recurrence-free rate in patients with H1 disease was higher than that in patients with H2 or H3 disease. Recurrence developed within 40 months of hepatectomy in most cases (Fig. 3).

Hepatectomy for H3 disease

Hepatectomy was undertaken in 32 patients with H3 disease and consisted of straightforward hepatectomy in 12 patients, preoperative PVE in eight, two-stage hepatectomy in two, and two-stage hepatectomy combined with PVE in ten. Adjunctive MCT was performed in one patient who had a straightforward hepatectomy, two with PVE, one with two-stage hepatectomy, and three with two-stage hepatectomy combined with PVE. The decision to perform multimodality treatment to avoid postoperative liver failure was made according to the specific clinical characteristics in each individual case, although, generally, a two-stage hepatectomy was used more often in cases of synchronous disease than in metachronous disease (Table 1).

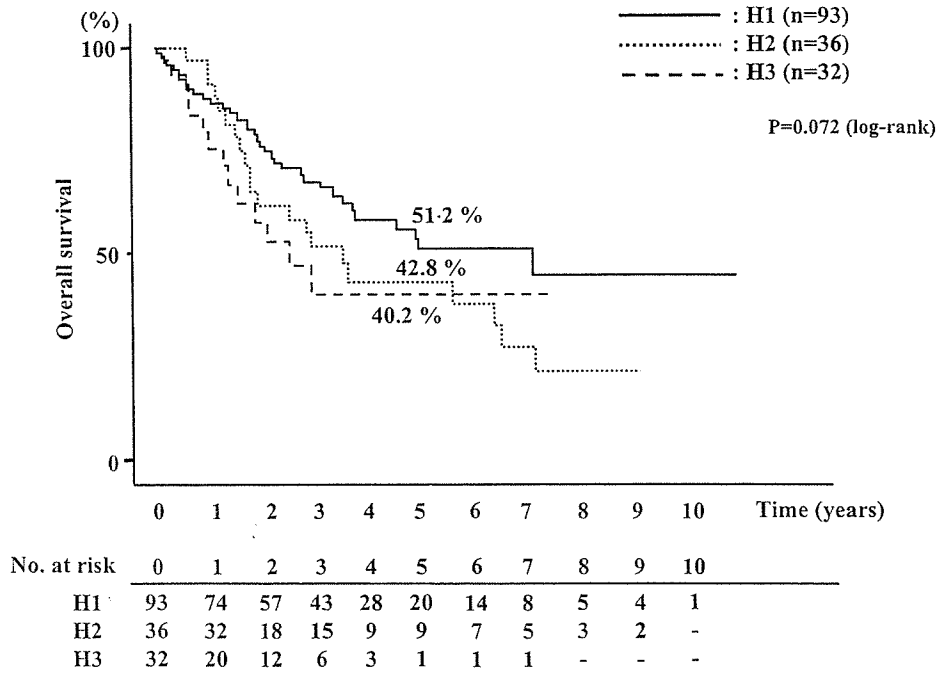

Fig. 2 Overall survival after hepatectomy for patients with liver metastases from colorectal cancer (*H1* uni-lobar disease, *H2* bi-lobar disease ≤4 lesions, *H3* bi-lobar disease ≥5 lesions)

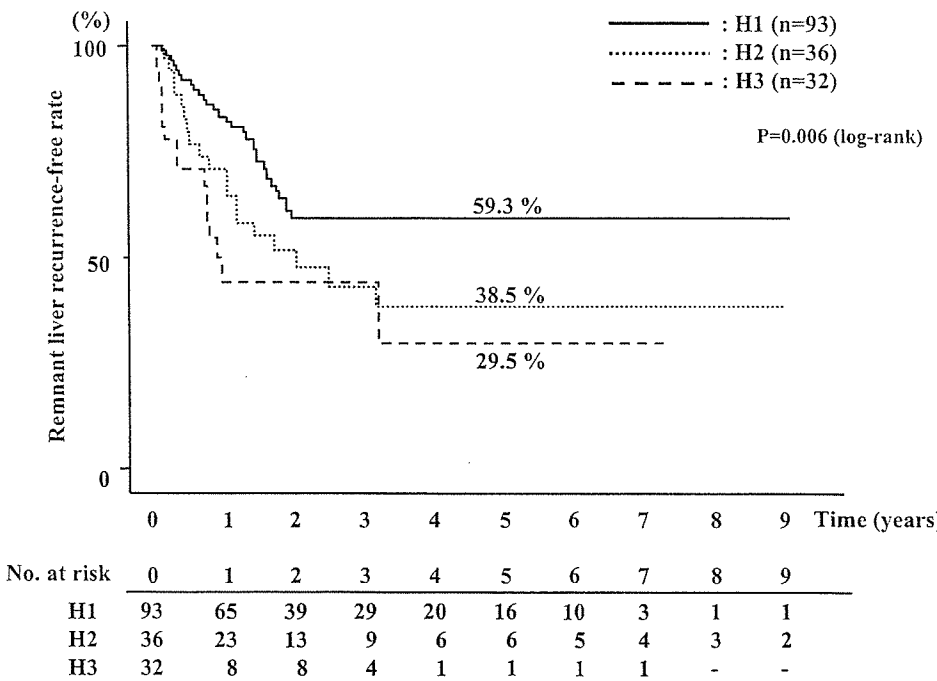

Fig. 3 Remnant liver recurrence-free rate after hepatectomy for colorectal cancer liver metastases. (*H1* uni-lobar disease, *H2* bi-lobar disease ≤4 lesions, *H3* bi-lobar disease ≥5 lesions)

Of the 12 straightforward hepatectomies, right hepatectomy, extended right hepatectomy, or right trisegmentectomy with partial resection of the contralateral lobe, was performed in three patients, left hepatectomy or extended left hepatectomy with partial resection of the contralateral lobe in three, central bi-segmentectomy in one, and multiple subsegmentectomy with partial resection in five. Seven of these 12 patients are alive, with a mean survival time (MST) of 22.4 months.

The eight hepatectomies performed after PVE involved right hepatectomy, right extended hepatectomy or right trisegmentectomy with partial resection of the contralateral lobe in five patients, left hepatectomy with partial resection in one, and multiple segmentectomy with

Table 1 Hepatectomy procedures in patients with H3 disease in chronological relation to primary resection

Procedure	Liver metastases	
	Synchronous	Metachronous
Straightforward (12)	9	3
Hepatectomy with PVE (8)	6	2
Two-stage hepatectomy (2)	2	0
Two-stage hepatectomy with PVE (10)	9	1

partial resection in two. Four patients are alive with a MST of 18.7 months.

Two-stage hepatectomy involved partial resection as the initial hepatectomy and right hepatectomy with partial resection of the left lobe as the second hepatectomy in one patient, and partial hepatic resection followed by left hepatectomy with partial resection of the right lobe in the other patient. One patient died of disease 26 months after the second hepatectomy, and the other is alive with no evidence of disease 52 months after the second procedure.

Ten patients underwent two-stage hepatectomy in which PVE was performed during the first hepatectomy. The initial procedure was partial or segmentectomy followed by right or extended right hepatectomy in seven patients, right hepatectomy followed by lateral segmentectomy in one patient, left hepatectomy followed by right segmentectomy with partial resection in one patient, and right partial resection followed by extended left hepatectomy with partial resection of the right lobe in one patient. Six of the ten patients are alive, with a MST of 25.5 months.

Survival of patients with H3 disease who underwent hepatic resection

The operating mortality rate of resection for H3 disease was 0%, and the morbidity rate was 15.2% (5/33: abdominal abscess in two patients, hyper-bilirubinaemia in one, and biliary fistula in two). The 1-, 3-, and 5-year survival rates were 79.5%, 57.6%, and 40.2%, respectively. On the other hand, the corresponding survival rates of patients who did not undergo hepatectomy were 47%, 8%, and 5%, respectively (data not shown). This difference was significant ($P<0.01$).

When the characteristics of the patients with H3 disease who underwent hepatectomy with and without NAC were compared, the former group had more extra-hepatic metastases than the latter ($P=0.043$) (Table 2). Five patients with NAC had extra-hepatic diseases: these were three cases of lung metastasis, one local failure and one case of both lung metastasis and peritoneal dissemination. Curative resection of extra-hepatic lesions was performed in four out of these five patients. Complete resection of peritoneal disseminated tumours was per-

Table 2 Demographic and clinical characteristics of patients with H3 disease who underwent hepatectomy. *P* values for the primary site and the hepatectomy (*Hx*) procedure were calculated by the χ^2 test, the others by Fisher's exact test. *HAI* intra-arterial chemotherapy via the hepatic artery

Variable		Neoadjuvant HAI (+) (n=12) n (%)	Neoadjuvant HAI (−) (n=20) n (%)	*P*
Primary lesion				
Duke's stage	B	1 (8.3)	5 (25.0)	0.370
	C	11 (91.7)	15 (75.0)	
Site	Colon	9 (75.0)	9 (45.0)	
	Rectum	3 (25.0)	9 (45.0)	0.202
	Colon and rectum	0 (0.0)	2 (10.0)	
Histology	Well differentiated	6 (50.0)	8 (40.0)	
	Moderately differentiated	6 (50.0)	12 (60.0)	0.718
Liver metastases				
Type	Synchronous	9 (75.0)	16 (80.0)	>0.999
	Metachronous	3 (25.0)	4 (20.0)	
Size	<60 mm	11 (91.7)	14 (70.0)	0.212
	>60 mm	1 (8.3)	6 (30.0)	
Concomitant extra-hepatic metastases	Present	5 (41.7)	2 (10.0)	0.074
	Absent	7 (58.3)	18 (90.0)	
Treatment-related variables				
Hx procedure	Straightforward Hx	7 (58.3)	5 (25.0)	0.014
	Hx with PVE	0 (0.0)	8 (40.0)	
	Two-stage Hx	2 (16.7)	0 (0.0)	
	Two-stage Hx with PVE	3 (25.0)	7 (35.0)	
Adjunct MCT		4 (33.3)	3 (15.0)	0.379
Tumour-free margin	<5 mm	10 (83.3)	14 (70.0)	
	>5 mm	2 (16.7)	6 (30.0)	0.676
Post-Hx HAI (total dose of 5-FU)	<5 g	5 (41.7)	9 (45.0)	
	>5 g	7 (58.3)	11 (55.0)	>0.999

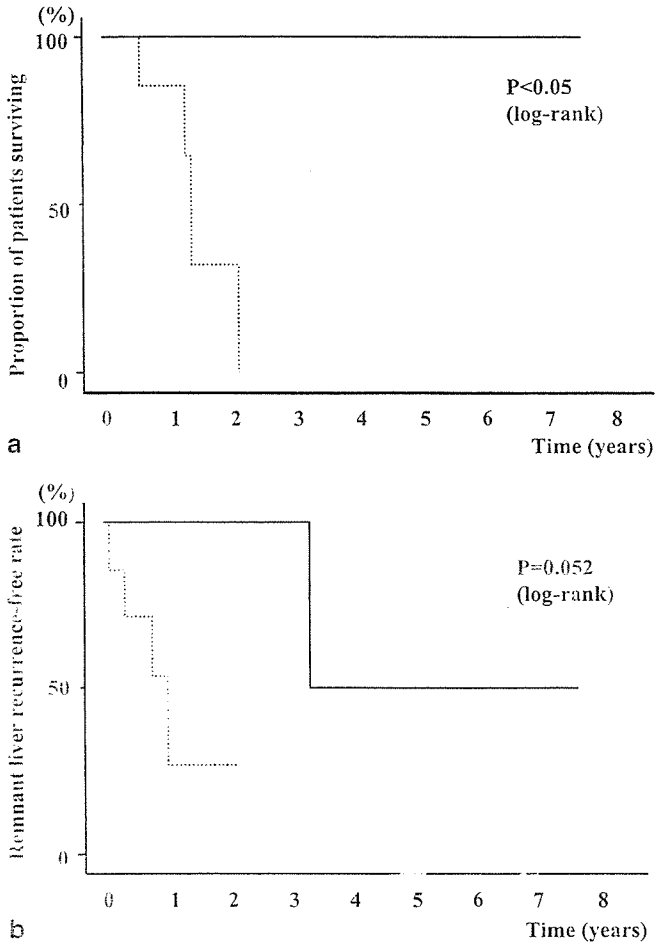

Fig. 4 Overall survival (**a**) and remnant liver recurrence-free rate (**b**) in patients who underwent neoadjuvant chemotherapy

formed in another patient with concomitant bilateral lung and peritoneal disease, but the lung lesions could not be completely removed in this patient. Two patients without NAC had lung metastases. Complete removal of the lung lesions was performed in one of these patients.

During the first hepatectomy, the median blood loss during hepatectomy was 1,183 ml (range 200–3,700) in the NEO^+ group, and 1,300 ml (range 230–3,279) in the NEO^- group. The median hospital stays for the two groups were 30 days (range 14–50) and 20 days (range 13–66), respectively. When a two-stage hepatectomy was performed, the median blood loss and the hospital stay at the second hepatectomy were 1,600 ml (range 670–7,000) and 21 days (range 14–43) for the NEO^+ group, and 975 ml (range 750–1,300) and 20 days (range 13–43) in the NEO^- group, respectively. The two groups were similar in terms of intraoperative blood loss and length of hospital stay postoperatively, after the first and second hepatectomies.

The 1- and 3-year overall survival rates after hepatectomy in the NEO^+ group were 90.9% and 46.8%, as against 67.2% and 37.2% in the NEO^- group, respectively. The 1- and 3-year recurrence-free rates for the remnant liver after hepatectomy in the NEO^+ group were 57.8% and 28.9%, but were 34.7% and 34.7% in the NEO^- group, respectively. Survival and recurrence-free rates for the remnant liver were also similar in the two groups.

The overall response rate of patients with NAC was 41.7%. When the patients who had received NAC were subdivided into responders (n=5) and non-responders (n=7), survival of responders, who were all disease free, was higher than that of non-responders (P<0.05). The recurrence-free rate for the remnant liver tended to be higher among responders than non-responders (P=0.052) (Fig. 4).

Discussion

Several reports have established the efficacy of surgical resection for solitary or few hepatic metastases from colorectal cancer [12, 13, 14, 15]. However, the literature regarding resection of four or more metastatic lesions is contradictory. Cady et al. [16] reported that no patient with three or more metastatic lesions had survived disease-free for more than 48 months. Fong et al. [12] reported that the presence of multiple metastases is an adverse prognostic factor from a prognostic score based on the outcome of 1,001 patients who underwent hepatic resection at a single institution. On the other hand, Scheele et al. [13] reported that the number of metastatic lesions did not predict outcome, provided that a tumour-free margin of resection was achieved. Minagawa et al. [1] also reported that patients with single nodules and those with four or more lesions achieved better 10-year survival rates than patients with two or three metastases.

The predictive value of the number of lesions for survival has been controversial and, at times, contentious, in the international surgical community. The discussion has focused on the cut-off number of four metastases. For some authors, this number represents the boundary between patients who are capable of achieving an acceptable outcome and those who are not [15, 16, 17]. In other reports, the number of patients who underwent resection of more than four nodules was too small to permit a meaningful evaluation of the data, or the resections were not considered curative in most cases. [13, 18]. In our study, the long-term survival of patients with five or more bi-lobar tumours was similar to that of patients with uni-lobar or four or fewer bi-lobar tumours. This finding is consistent with the report by Minagawa et al. [1], despite a high frequency of hepatic recurrence. Therefore, we believe that even patients with five or more bi-lobar tumours should not be denied curative resection if it is technically feasible. This treatment strategy has not

changed in our institution since 1992. The importance of this conclusion is underlined by considering the poor outcome of patients treated with chemotherapy alone in whom the 2-year survival rate is only 15% [19, 20]. However, Gayowski et al. [15] and 23% of the authors in the paper reported by Minagawa et al. [1] considered bi-lobar involvement a poor prognostic factor [15, 18]. Our results suggest that hepatic resection improves survival in selected patients with bi-lobar metastases.

Safety was an important consideration in resection of multiple bilateral metastases, particularly with regard to margin clearance and postoperative hepatic function. When we were concerned that the amount of liver tissue remaining after curative resection would be inadequate, i.e. less than 30 to 40% of the liver [21], we used two supplemental techniques. PVE was performed to induce atrophy of the liver to be resected and induce hypertrophy of the liver to be left. The same principle underlines two-stage hepatectomy, in which a lateral segmentectomy may be followed by a right hepatectomy. Azoulay et al. [21] reported that preoperative PVE of the right lobe induced an increase in the remnant liver volume, from 26±6% to 37 ± 8%, and Kawasaki et al. [22] reported that PVE of the right side increased the left side volume to 24%. We [23] also have reported that preoperative PVE not only induces hypertrophy but also improves function of the contralateral lobe. Once hypertrophy of the contralateral lobe had occurred following PVE, all eight patients were considered to have sufficient remnant liver, based on volumetric assessment, to tolerate the initial planned resection, and the actual clinical courses after extended liver resection were uneventful.

When multiple bilateral metastases are present, safe curative resection is not always possible, even with PVE. In such cases, the two-stage procedure, which provides a safer and potentially more curative hepatectomy, was used. The initial hepatic resection was intended to remove as many metastases as possible, even though not all could be resected. After the remnant liver had undergone hypertrophy, secondary hepatectomy was performed only when it was potentially curative, i.e. there was no tumour progression, and adequate residual parenchyma.

Bismuth et al. [24] reported that the secondary hepatic resection can be performed with little surgical mortality [1, 11], 36% clear surgical margins and a 5-year survival rate of 40%. Adam et al. [25] found that a two-stage hepatectomy was feasible in 13 of 16 patients. The mortality rate was 0% for the first hepatectomy, and 15% for the second. The 3-year survival rate was 35%, and median survival was 31 months after the second hepatectomy. We agree with Adam et al. that a two-stage hepatectomy may induce long-term survival in selected patients with unresectable multiple metastases by straightforward hepatectomy, and increase the percentage of patients with resectable disease.

In the present study, MCT was performed as an adjunct to several types of hepatectomy in seven of the 32 patients with multiple bi-lobar liver metastasis. MCT was initially reported in 1986 [26] as a form of thermal ablation therapy. It was also reported that the long-term outcome of patients with liver metastases treated by MCT was comparable to that of patients treated by hepatectomy [27]. Complete necrosis of metastatic liver tumours was reported to have been achieved in more than 80% of cases [28]. At present, this technique is considered to be a promising therapy for patients who are not suitable for hepatic resection or as an adjunct to liver surgery.

Unfortunately, recurrences still occurred in two-thirds of patients after hepatectomy. In the current study the survival rate of patients who achieved at least PR following chemotherapy was higher than patients who did not. This outcome suggests that suppression of subclinical lesions and micrometastases by NAC is necessary to produce a survival effect for hepatectomy in patients with H3 disease. NAC had no effect on hepatic recurrence or any survival benefit. However, patients who responded to NAC did have better survival. Therefore, we need to establish some objective determinate of the chemosensitivity of each patient.

Although several studies suggested that adjuvant hepatic arterial chemotherapy had not reliably translated into an overall survival benefit after hepatectomy, it yielded significant improvements in hepatic recurrence [29, 30]. Furthermore, the response rate to this treatment was usually higher than that to systemic chemotherapy [31]. Therefore, we performed hepatic arterial chemotherapy on multiple bi-lobar liver metastasis as a neoadjuvant measure. On the other hand, with regard to the problem of the high rate of extra-hepatic recurrence after hepatectomy, we may reconsider replacing adjuvant hepatic arterial chemotherapy after hepatectomy with hepatic arterial chemotherapy together with systemic chemotherapy in the manner previously reported [29].

Bismuth et al. [24] and Giacchetti et al. [32] reported that the benefit of chemotherapy to patients who respond favourably to it has been incompletely explored and that it may allow secondary resection of liver metastases when curative primary resection is impossible. It is unclear whether preoperative chemotherapy, postoperative chemotherapy, or both, is the most efficacious. The present review does suggest, however, that some form of adjuvant chemotherapy will emerge as the best treatment for resectable liver metastases, especially when multiple lesions are present bilaterally.

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Original Paper

Adjuvant Hepatic Arterial Infusion Chemotherapy after Curative Resection for Dukes C Colorectal Cancer: A Pilot Study

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KEY WORDS:
Colorectal cancer; Hepatic arterial infusion chemotherapy; 5-fluorouracil; Liver metastasis

ABBREVIATIONS:
Hepatic Arterial Infusion (HAI); Hepatic Arterial Infusion Chemotherapy (HAIC); 5-Fluorouracil (5-FU)

ABSTRACT

Background/Aims: The aim of this study was to evaluate the effect and the toxicity of prophylactic adjuvant hepatic arterial infusion chemotherapy (HAIC) on liver metastases and on overall survival of Dukes C colorectal cancer patients.

Methodology: Ninety patients in whom Dukes C colorectal cancer was diagnosed and were treated with curative resection between 1993 and 1997 underwent HAIC. The HAIC regimen consisted of a 24-hour continuous infusion of 1500mg of 5-fluorouracil, administered once a week for 8 weeks, utilizing a portable infusion drug delivery system to ambulatory patients. Patients to whom 7g or more of 5-fluorouracil could be given were included in the HAIC group, which resulted in 70 of the 90 patients being in this group. The HAIC group overall survival and liver recurrence rates were compared with those of 62 non-treated cases of Dukes C, which formed the non-HAIC control group.

Results: There were no serious toxic effects in this study. Significant differences were seen in the cumulative overall 5-year survival (HAIC group, 84.1%; non-HAIC group, 65.2%; $p=0.0369$). The cumulative 5-year liver metastasis-free rate was 92.7% in the HAIC group and 78.6% in the non-HAIC group ($p=0.0649$). In cases of distal lymph node metastasis, a risk factor for liver metastasis, the cumulative 5-year liver metastasis- free rate in the HAIC group (91.7%) was significantly higher than that in the non-HAIC group (58.6%; $p=0.0268$).

Conclusions: HAIC effectively prevents metachronous liver metastasis, especially in patients with pre-existing distal lymph node metastases, and improves the prognosis of advanced colorectal cancer.

INTRODUCTION

In Dukes C colorectal cancer, even when curative surgery is performed, the overall 5-year survival is only around 60% because of tumor recurrence. The liver is the most frequent site of recurrence, accounting for 40 to 50% of all colorectal cancer recurrences (1). The best treatment for liver metastases of colorectal cancer is major hepatic resection. The 5-year survival rate of cases with curative resection for liver metastasis is 25% (2), but in fact, only 10 to 20% of patients with liver metastases undergo surgical treatment. An effective adjuvant treatment should therefore be devised to prevent liver metastases.

Metachronous liver metastasis may arise from microscopic metastases that are undetected at initial surgery. Otherwise, it may originate from tumor cell emboli reaching the portal system via the mesenteric vein during the initial surgery. Consequently, previous studies have advocated portal injection of cytotoxic agents at the time of surgery and during the postoperative period to prevent metachronous liver metastasis (3,4). However, a large randomized trial of portal vein infusion of fluorouracil and heparin showed that they had no significant impact on survival (5).

In the present study, we investigated whether adjuvant hepatic arterial infusion chemotherapy could reduce the incidence of metachronous liver metastasis and prolong patient survival.

METHODOLOGY

At Yokohama City University Hospital, from 1993 to 1997, out of 191 patients with histologically confirmed Dukes C colorectal cancer who had had curative surgery, 90 patients received adjuvant hepatic arterial infusion therapy. Informed consent was obtained preoperatively from all patients eligible for the trial. Physical examination, computed tomography of the abdomen and pelvis, chest radiography or computed tomography were performed so as to demonstrate that there was no evidence of synchronous liver metastasis or other distant metastases.

During the operation, ultrasound sonography was also performed to confirm that no liver metastases were present. At the time of pump insertion, cholecystectomy was performed if it had not been done previously. The tip of an arterial catheter was placed at the point where the gastroduodenal artery branched off from the common hepatic artery. The right gastric

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