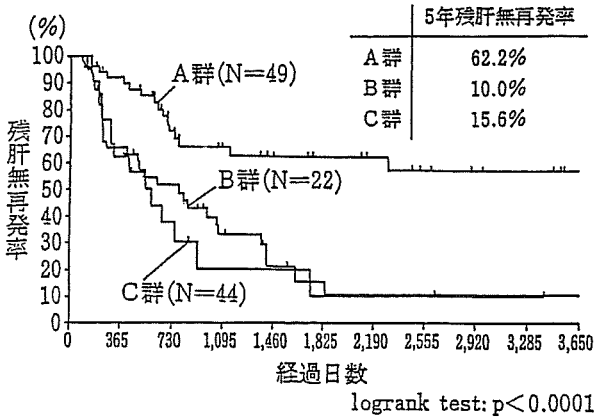


図4 同時性肝転移肝切除後の投与量別残肝無再発曲線

量15 g 以上)との間で，有意に残肝再発の差を認め，肝動注療法の残肝再発予防効果を認めた．

一方異時性肝転移で検討すると，A 群：56.9%，B 群：62.3%，C 群：38.9%で，手術単独でも残肝再発は比較的低く，肝動注療法による残肝再発の予防効果は低いと思われた．図5は肝切除後の残肝再発率の比較である．予想通り同時性ではA群の残肝再発率が有意に低く，肝動注療法による微小肝転移の予防効果を裏づけるものであった．図6は肺転移を中心とする肝外再発の発生頻度を比較したものであるが，同時性肝転移，異時性肝転移いずれも高率に認め，肝切除後のさらなる予後向上のためには，肝切除後の全身化学療法の必要性を認めた．このように，大腸癌肝転移で切除可能な症例でも，同時性か異時性かで，肝切除後の再発状況が大きく異なることを把握することは，大腸癌の治療戦略を考える上で，重要なことであると考える．

表2は，肝切除例の残肝再発に対する多変量解析を Cox の比例ハザードモデルで行ったが，同時性・異時性，肝転移の程度，肝動注療法の程度，原発巣のリンパ節転移の有無が有意な因子であった．

以上の結果から，同時性肝転移に対しては，肝転移切除後に肝動注療法および全身化学療法を併用することが延命のためには重要であると思われた．

## II. 大腸癌切除不能同時性肝転移に対する治療

大腸癌切除不能肝転移の非治療例の自然経過は一般的に4.5ヵ月とされている[3]．最近，全身化学療法の進歩により，治療効果が向上し，同時性肝転移で，肝切除不可能な症例に対して，原発巣を切除するかどうか，意見が分かれるところである．数年前までは原則的に原発巣は切除する施設が大部分を占めていたが，FOLFOX を中心とする併用療法により原発巣ばかりか肝転移に対しても，

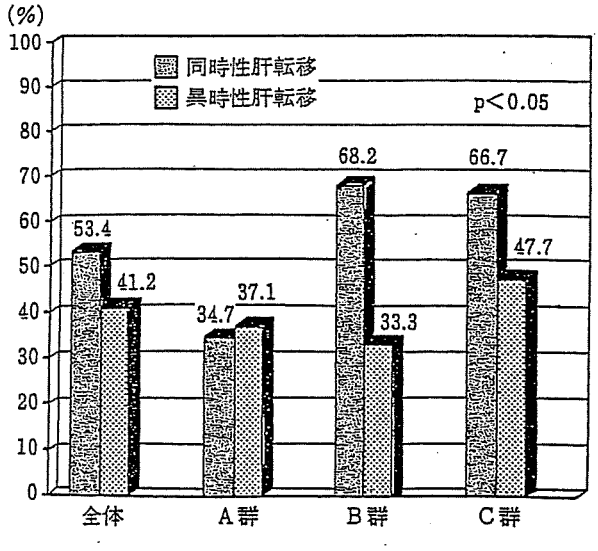


図5 肝動注療法の程度別残肝再発率の比較

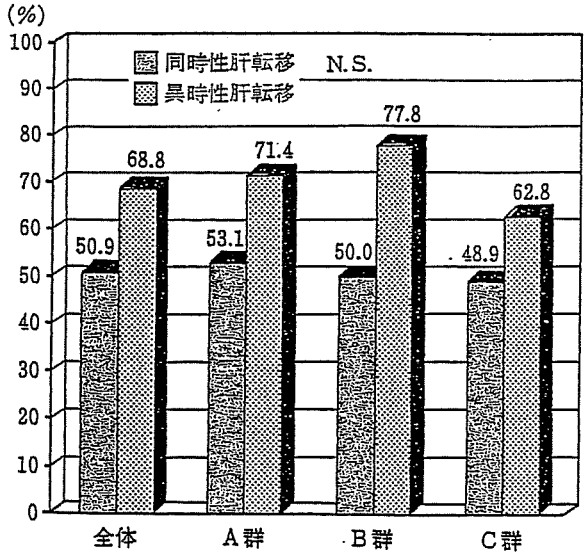


図6 肝動注療法の程度別肝外再発率の比較

表2 残肝再発に対する多変量解析(Coxの比例ハザードモデル)

| 予後因子 | リスク比 | p値 | 95% CI |
|---|---|---|---|
| 性別 F：M | 0.7919 | 0.3678 | 0.4765～1.3159 |
| 同時性：異時性 | 0.5270 | 0.0202 | 0.3069～0.9050 |
| 肝外再発なし：あり | 1.5169 | 0.1224 | 0.8940～2.5738 |
| $H_1$：$H_2$ | 2.1019 | 0.0174 | 1.1396～3.8769 |
| $H_1$：$H_3$ | 0.3535 | 0.3145 | 0.0466～2.6815 |
| HAI 15g未満：15g以上 | 0.4820 | 0.0529 | 0.2302～1.0093 |
| 15g未満：施行せず | 1.2712 | 0.4610 | 0.6716～2.4062 |
| 肝切除法 系統：部分 | 1.3442 | 0.2639 | 0.8000～2.2586 |
| 組織型 well：well以外 | 0.8093 | 0.4329 | 0.4770～1.3733 |
| TW 2mm未満：2mm以上 | 0.7800 | 0.4360 | 0.4174～1.4576 |
| n0：n1以上 | 1.8866 | 0.0431 | 1.0199～3.4902 |

40～50%の奏効率を示し，無理に原発巣を切除しなくても，イレウスや出血等の原発巣の進展に伴う症状の出現する頻度が減少していることがその理由の一つであると思われる．しかし切除不能肝転移に対して，原発巣を切除するかどうかについて結論を出すのは，時期尚早で，症例の集積が必要であると思われる．

一方，切除不能肝転移に対して，化学療法を施行後に切除可能なった時点で肝切除を行う報告[4)-5)]も増え，世界的にも認められた治療方法の一つになっている．

われわれも，切除不能肝転移に対して，図7のようなメニューで持続肝動注療法を施行し，肝転移が縮小した時点で，積極的に肝切除を行った．図8のように，動注後に肝切除が可能となった動注後肝切除群の3年生存率は39.1%で，5年生存率は16.3%で，肝動注療法だけに終わった群の4.3%，0%に比較し，有意に($p<0.0001$)延命効果を認めた．肝動注後に肝切除をした症例の肝切除標本であるが，変性壊死を起こした肝転移巣内にviable cellの集塊をみることはしばしばあり，CT上CRと判定されても，がん細胞を完全に死滅させることは不可能であり[4)]，肝転移の再燃を防止するために肝切除が可能になった時点で肝切除を行うことは延命に寄与できる方法の一つであると思われる．

肝切除後の残肝再発は高頻度に出現するため，可能なら肝動注療法を継続するが，手術後はカテーテルの閉塞等で継続できないことも多い．また図9に示すように，肝外再発も高頻度に出現することから，肝切除後も全身化学療法を継続して実施することは重要であると思われる．

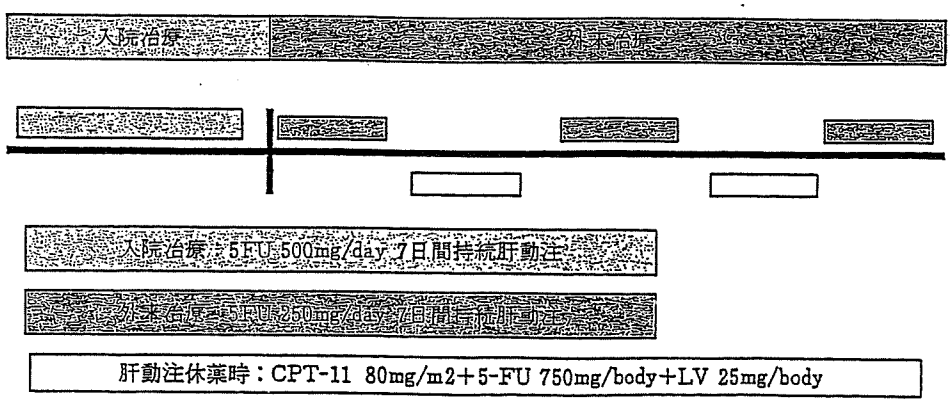


図7 大腸癌切除不能転移例に対する持続肝動注療法

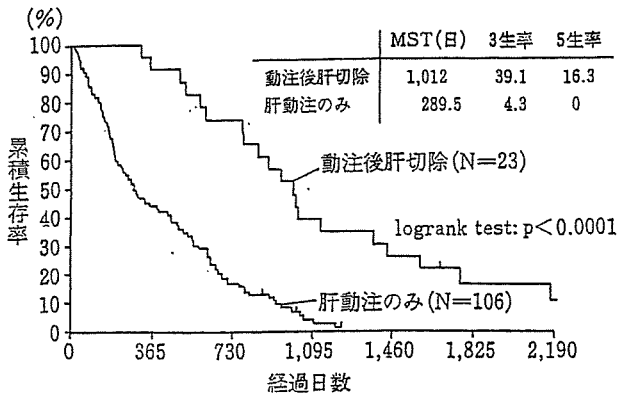


図8　$H_3$肝転移動注後肝切除の有無別の予後

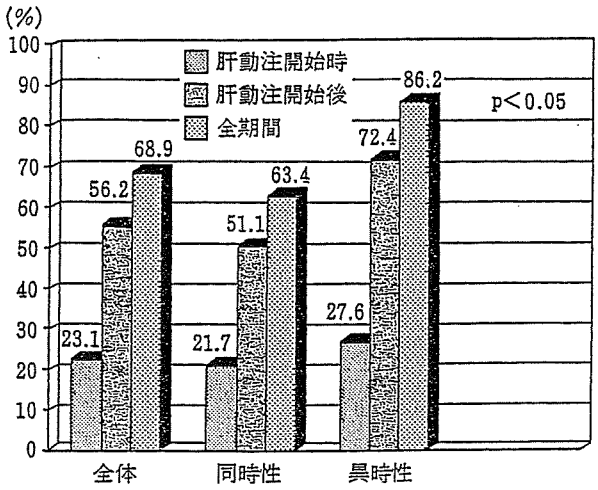


図9　肝外再発の発生頻度

## III. 大腸癌同時性肝転移に対する治療方針

大腸癌同時性肝転移に対する治療方針を図10にまとめた．肝転移を認めた時点で，肝切除が可能であるかどうか，CTおよびMRI(SPIO-MRI)で肝転移の個数および局在を確認し，肝切除可能なら，肝切除を行うが，同時性肝転移では肝切除術後の微小肝転移と肝外転移を予防するため，肝動注療法および全身化学療法の併用を行う．肝動注療法の実施が不可能な場合は全身化学療法を選択する．FOLFOXまたはFOLFIRIの方が強力な治療方法であると思われるが，現時点では予防投与としてのFOLFOXやFOLFIRIは一般には認められておらず，UFT＋LV(経口)または5-FU＋LV (RPMI)[6]の全身化学療法を選択している．肝切除後の症例は通常の大腸癌の治癒切除に比べ再発の高危険群であると考えられ，いずれ予防投与の抗がん剤のメニューも変化し，FOLFOXやFOLFIRI等のより強力な化学療法に変

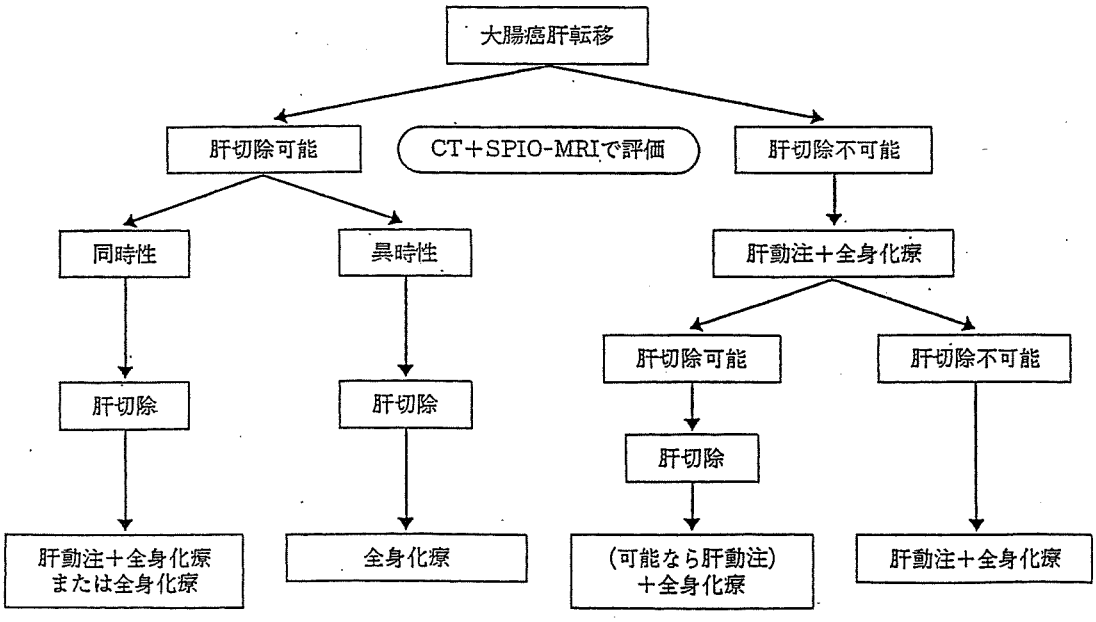


図10　大腸癌肝転移に対する治療戦略

わる可能性があると思われる．

肝切除が不可能であると判断された場合は，肝動注療法と全身化学療法を併用し，肝転移の縮小および肝外転移の出現を予防し，肝切除が可能になったところで肝切除を行い，肝切除後も可能な限り肝動注療法と全身化学療法の併用を継続する(ただし肝動注の継続が不可能なら全身化学療法のみを行う)．肝切除が不可能なら，引き続き肝動注療法と全身化学療法の併用を継続する．

## おわりに

大腸癌同時性肝転移は，原発巣と転移巣を病状の進展と全身状態を考慮して，個々の症例で治療法を選択する必要があると思われる．化学療法も近年の併用療法の進歩により，全身化学療法でも肝動注療法に匹敵する治療効果が得られるようになり，また肝動注療法の管理の難しさから，欧米では分子標的治療を併用した全身化学療法が推奨されるようになってきている[7]．しかしCRが得られるような治療効果が得られないにもかかわらず莫大な医療費がかかるようになり，大きな問題となっているのも事実である[8]．肝単独の治療効果とその切れ味を考慮すると，肝動注療法は捨てがたい治療手段である．肝転移が直接的な生命予後規定因子になった場合や全身化学療法で治療効果が期待できなかった場合，肝動注療法で治療効果が期待できる可能性は完全に否定できないのである．新薬に振り回されることなく，患者の予後規定因子が何かをよく見極め，原発巣の治療と肝転移の治療方法を選択するバランス感覚が必要とされる疾患であることを認識し，治療に当たるべきである．


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# Outcomes of hepatic artery infusion therapy for hepatic metastases from colorectal carcinoma after radiological placement of infusion catheters

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**Abstract**

*Aim*: The aim of this study is to evaluate the safety and efficacy of hepatic artery infusion (HAI) of 5-fluorouracil (5FU) for patients with liver metastases from colorectal carcinoma after radiological placement of infusion catheters.
*Methods*: Forty-two patients with liver metastases from colorectal carcinoma received radiological placement of infusion catheters using the distal fixation method. They received continuous HAI of 5FU 1000–1500 mg for 5 h weekly or biweekly. Tumor status was assessed by chest-abdominal computed tomography (CT) scan after every 10 infusions. Hepatic perfusion was checked by CT arteriography via the infusion port after every 10 infusions.
*Results*: Radiological placements of catheters were performed successfully in all cases. Each patient received an average of 36 treatments (range: 10–98). Catheter failure was found in 3 patients (7.1%). Nine incidents of grade 1 toxicity were observed in 8 patients (19.0%). There was a complete response in 6 patients, partial remission in 18, stable disease in 9, and progression of disease in 9 (response rate: 57.1%). Overall median survival time was 29.1 months. Using Cox's proportional hazard model, lymph node metastases in primary colorectal carcinoma and pre-treatment serum CEA affected overall survival ($P = 0.011$, $P = 0.005$).
*Conclusions*: HAI after radiological placement of infusion catheters is a safe and effective treatment particularly for patients with no lymph node metastasis in primary carcinoma or with a low pre-treatment serum CEA level.


*Keywords:* Median survival time; Response rate; Toxicity; CEA; Lymph node metastases; Arteriography; Infusion port; Distal fixation method

## Introduction

Hepatic metastasis is one of the serious events that determine the prognosis of patients with advanced colorectal carcinoma. Surgical resection alone can result in significant prolongation of survival in patients with favorable prognostic factors. The 5-year survival rate of patients who underwent resection of hepatic metastases was reported to be 30% to 40%.[1,2] Chemotherapy is used to treat hepatic metastases in colorectal carcinoma patients when surgical resection cannot be performed. A number of phase 3 clinical trials have reported median survival times of nearly 20 months using combination chemotherapy with 5-fluoruracil (5FU), leucovorin (LV), oxaliplatin or irinotecan for metastatic colorectal carcinomas.[3–5] However, these systemic chemotherapy regimens cause a higher incidence of clinically significant toxicities and make it difficult for patients to continue with treatment.

Randomized trials evaluating hepatic artery infusion (HAI) therapy for the treatment of unresectable hepatic metastases have demonstrated higher response rates (31%–50%) than those achieved with systemic chemotherapy (8%–20%), but no survival benefit was reported.[6,7] HAI offers a means for achieving high drug concentrations in liver metastases and low concentrations systemically.[8] HAI results in a high response rate for local control and is associated with a very low incidence of toxicities.[9] In

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order to obtain a sufficient therapeutic effect, HAI should be continued successfully without catheter failure. In most HAI studies, catheter placements were performed surgically. When placed surgically, catheter problems can result, which is one of the reasons why HAI was previously unsuccessful for improving survival. In 1992, a new radiological technique was developed in which a side-hole catheter is placed in the hepatic artery with the tip fixed in the gastroduodenal artery.[10] With this technique, the risk of catheter failure and toxicity is reduced. It has also been reported that computed tomography (CT) arteriography via the infusion port is useful for detecting hepatic perfusion abnormalities during HAI.[11]

Although hepatic metastases respond well to HAI treatment, extra-hepatic metastases or recurrence often appear and are important factors for defining the prognosis of HAI-treated patients. Since peripheral venous concentrations of 5FU are lower and plasma clearance rates are higher following HAI compared with a similar dose administered by intravenous infusion, HAI is less effective for controlling extra-hepatic metastases.[12] To maximize the therapeutic efficacy of HAI, patients who can benefit more from HAI than from systemic chemotherapy should be selected. However, prior studies of HAI have not identified the patient types for which HAI is indicated.

We placed infusion catheters for HAI radiologically in patients with liver metastases from colorectal carcinomas using the distal fixation method. Hepatic perfusion was checked by CT arteriography via the infusion port periodically. We administered 5FU by HAI as first-line therapy and examined the clinical safety and efficacy of HAI treatment. We also examined the status of liver metastases and the clinicohistological features of the primary colorectal carcinomas of HAI-treated patients in order to identify candidates most likely to benefit from HAI therapy.

## Patients and methods

### *Patients*

We included patients with liver metastases from colorectal carcinomas which were confirmed histologically. Their primary colorectal carcinomas were resected surgically between January 1998 and September 2005. Patients with extra-hepatic metastases, defined as pulmonary metastases or local recurrence, were excluded. Forty-two patients met the criteria and were enrolled in the study. Informed consent was obtained from all patients. HAI was started between November 1999 and October 2005. Response and survival rates were monitored for all patients.

### *Procedure of catheter placement*

Catheter placements in the hepatic artery were done radiologically by interventional radiologists. The side-hole catheters were placed using the distal fixation method.[10] The gastroduodenal artery and right gastric artery were embolized radiologically with coils before the catheter fixation. The tip of the catheter was fixed into the gastroduodenal artery and the side hole was placed in the common hepatic artery. The catheter was inserted via the right femoral artery and connected to the infusion port (Infuse-a-Port, Strato Medical Corp., Beverly, MA, USA). The port was implanted in the subcutaneous space.

### *Procedure of HAI*

HAI treatment was performed weekly or biweekly at an outpatient chemotherapy room. 5FU (1000–1500 mg) was dissolved in 200 ml of physiological saline and packed into a portable infusion pump (INTERMATE LV 50 ml/h; Baxter Healthcare Corp., Deerfield, IL, USA). Before every injection, the catheter and the port were flushed with 5 ml saline. HAI was performed continuously for 5 h. The catheter and the port were filled with 5000 units of heparin after each infusion. Hepatic perfusion was assessed by CT arteriography via the infusion port after every 10 infusions. The treatments were discontinued when the therapeutic response was judged as progressing disease (PD) or catheter failure. National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0 was used to assess toxicity.[13]

### *Clinical response evaluation*

Patients scheduled for HAI received a chest-abdominal CT scan before the start of treatment. Tumor status was assessed by chest-abdominal CT scan after every 10 infusions. The therapeutic response was evaluated according to RECEIST guideline.[14] Serum carcinoembryonic antigen (CEA) levels were also measured before treatment and after every 10 infusions.

### *Survival and statistical analysis*

Actuarial survival curves were computed by the Kaplan–Meier method. The survival rate results among the subgroups were analyzed by log-rank analysis. Cox's proportional hazard model was used to analyze differences in risk factors for survival using SPSS software version 14.0.

## Results

### *Patients and treatments*

Forty-two patients with liver metastases from colorectal carcinomas were enrolled for HAI treatment. The characteristics of the patients are shown in Table 1. Catheter placements in the hepatic artery and HAI treatments were performed successfully in all cases.

Each patient received an average of 36 treatments (range: 10–98). CT arteriography via the infusion port showed hepatic artery occlusion after 18 or 29 infusions

Table 1
Patients characteristic

| Characteristic | No. of patients | Characteristic | No. of patients |
|---|---|---|---|
| Sex | | pTNM of primary colorectal carcinoma | |
| Male | 27 | pT | |
| Female | 15 | pT1 | 0 |
| Age (average) | 65.8 | pT2 | 0 |
| Onset of liver metastases | | pT3 | 39 |
| Synchronous | 26 | pT4 | 3 |
| Metachronous | 16 | pN | |
| Previous hepatectomy | | pN0 | 12 |
| Yes | 3 | pN1 | 16 |
| No | 39 | pN2 | 14 |
| No. of liver metastases | | pM | |
| ≤4 | 27 | pM0 | 16 |
| 5≤ ≤9 | 7 | pM1 | 26 |
| ≥10 | 8 | Histology of primary colorectal carcinoma | |
| Serum CEA level | | Well | 13 |
| ≤50 | 23 | Moderate | 26 |
| 50< ≤300 | 8 | Poorly | 2 |
| >300 | 11 | Mucinous | 1 |

in 2 patients, and displacement of the catheter from the hepatic artery in 1 patient. These 3 patients (7.1%) discontinued the treatment. Collateral circulation from the right inferior phrenic artery to the liver was detected in 3 patients. They were embolized by coils radiologically in order to correct the intra-hepatic perfusion of 5FU and the treatments were restarted.

*Toxicity*

Nine incidents of grade 1 toxicity were observed in 8 patients. No grade 2–4 toxicity was observed. The rate of chemotherapy-related toxicity due to HAI was 19.0% (8/42).

*Therapeutic response rate to HAI*

We evaluated the therapeutic response to HAI by CT scanning according to RECEIST guidelines. Complete response (CR) in 6 patients, partial remission (PR) in 18 patients, stable disease (SD) in 9 patients, and PD in 9 patients were observed. The overall response rate was 57.1%. Extra-hepatic metastases appeared in 22 patients and in these cases HAI was switched to systemic chemotherapy.

In relation to lymph node involvement in primary colorectal carcinoma, the response rate was 66.7% in pN0, 50.0% in pN1, and 57.1% in pN2. The differences between groups were not statistically significant. No significant differences in the response rate were observed in relation to the histology of primary carcinomas or pre-treatment serum CEA levels. Thirty-three of 42 patients showed elevated (>5.0 ng/ml) serum CEA levels prior to treatment. A CEA decline of 50% or more in patients who had increased baseline CEA levels was observed in 26 patients (78.8%).

*Survival of patients treated by HAI*

The overall median survival time (MST) was 29.1 months. We examined survival rates in relation to lymph node involvement in primary colorectal carcinoma. MST was 50.1 months in pN0 and 23.2 months in pN1-2. The survival rate in patients with pN0 was significantly higher than in patients with pN1 or pN2 ($P = 0.011$) (Fig. 1). The survival curves did not differ significantly in relation to the number of hepatic metastases prior to treatment ($P = 0.60$). We also examined MST in relation to pre-treatment serum CEA levels. MST was 36.3 months in patients with serum CEA ≤50 ng/ml and 24.1 months in patients with serum CEA >50 ng/ml ($P = 0.01$). No significant difference was observed between the subgroups of patients with synchronous and metachronous liver metastases ($P = 0.33$). Furthermore, the histological features of the primary carcinoma did not differ significantly between the subgroups. Multivariate analysis showed lymph node metastases of primary colorectal carcinoma (pN) and pre-treatment serum CEA to be significant risk factors ($P = 0.017$ and $P = 0.004$, respectively) (Table 2).

## Discussion

*HAI and systemic chemotherapy for liver metastases from colorectal carcinomas*

We administered 5FU by HAI in patients with liver metastases from colorectal carcinoma after radiological placement of infusion catheters using the distal fixation method. The overall response rate and MST were better than those of the systemic chemotherapy reported. Prior studies of systemic chemotherapy included patients who had extra-hepatic

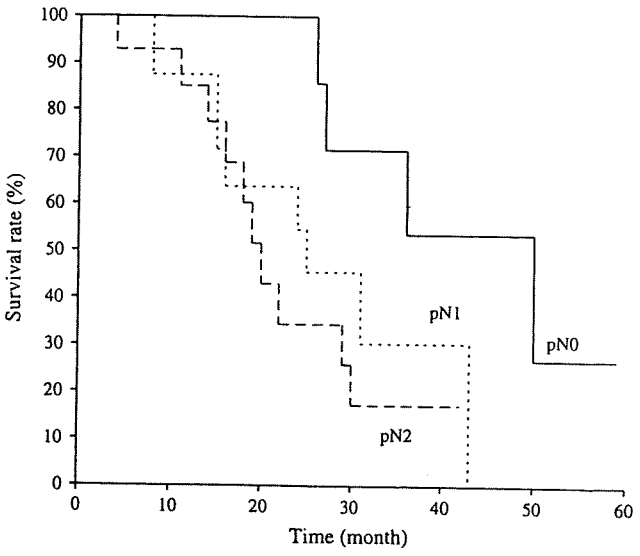


Figure 1. Survival curves according to pN stage of primary colorectal carcinoma. Significant differences were seen between pN0 and pN1 ($P < 0.001$) and between pN0 and pN2 ($P < 0.001$).

Table 2
Multivariate analysis of risk factors for overall survival

| Risk factor | Hazard ratio | 95% CI | *P* value |
|---|---|---|---|
| pN0 vs. pN1–2 | 4.50 | 1.31–15.47 | 0.017 |
| Serum CEA ≤50 vs. >50 | 3.67 | 1.42–9.49 | 0.004 |

metastases or recurrences, and these patients had a worse prognosis than patients with hepatic metastases only. It is difficult to compare these results with our study, which did not include cases with extra-hepatic metastases. Kerr and associates reported a multicenter, randomized trial of HAI versus intravenous 5FU and LV for colorectal carcinoma liver metastases.[15] There was no significant difference in MST or progression-free survival. However the HAI group received a median of only 2 cycles, because of catheter failure, compared with 8.5 cycles for the intravenous group. Recently, Kemeny and associates reported the results of a randomized trial comparison between HAI using floxuridine and systemic chemotherapy using 5FU and LV.[16] Overall survival was significantly longer for HAI versus systemic treatment (median, 24.4 v 20 months). The median number of cycles received was 3 and 4 for the HAI and systemic arms, respectively. In cases where catheters are placed accurately and maintained without failure, the therapeutic response to HAI was deemed to be preferable for the treatment of liver metastases.

*Successful HAI with new techniques*

In order to continue HAI successfully without catheter failure, it is essential for interventional radiologists to be highly skilled in performing the procedure. When inserting the catheter, the branch vessels of the hepatic artery should be embolized accurately.[17] Otherwise, 5FU can flow into the stomach or pancreas and cause toxicity, such as nausea and vomiting, which can lead the physician to discontinue treatment. CT arteriography via the infusion port is useful for detecting abnormal perfusion during HAI. Collateral circulation from extra-hepatic vessels to the liver during HAI should be also embolized radiologically in order to correct for variations in intra-hepatic perfusion of 5FU.[18] The radiological placement of the catheter and careful follow-up using CT arteriography are essential for maintaining safe HAI.

*Prognostic factors of HAI*

MST was influenced by lymph node metastases of the primary colorectal carcinomas. Since HAI does not control extra-hepatic metastases, patients with lymph node metastases are not ideal candidates for HAI treatment but can be treated with systemic chemotherapy. Elevated CEA levels are indicative of advanced-stage liver metastases, as suggested by our finding that CEA levels influenced MST. The response rate was not influenced by histological features or lymph node metastases of primary colorectal carcinomas in our study. Also, the response rate was not influenced by the synchronous/metachronous status of liver metastases, the number of hepatic metastases, or pretreatment serum CEA levels. It has been reported that enzymes involved in 5FU metabolism, such as thymidine synthase and dihydropyrimidine dehydrogenase, are important predictors of the therapeutic efficacy of 5FU.[19,20]

*Indications for HAI*

In this study, we demonstrated that patients with pN0 in primary colorectal carcinoma or a lower serum CEA level before treatment exhibited the longest MSTs. These patients, therefore, are suitable candidates for HAI therapy. Because HAI resulted in a very low toxicity rate, it can be applied as second-line therapy for patients who have discontinued systemic chemotherapies due to toxicity but still have life-threatening liver metastases. In order to maximize the therapeutic effectiveness of HAI, it is important to continue HAI with well-controlled delivery of 5FU without catheter failure or toxicity.

*Improvement of HAI*

In order to improve the therapeutic efficacy of HAI, new approaches are developing in 2 directions. One of these approaches involves the use of new therapeutic agents.[21] New combinations of 5FU, folinic acid, and interferon-α have been used with HAI and high tumor response rates have been reported.[22] The other approach involves the use of HAI and systemic chemotherapy in combination.[23] Adjunctive systemic chemotherapy can compensate for one of the weakness of HAI; i.e., HAI is completely ineffective for the treatment of extra-hepatic metastases. However it has been reported that combined treatment with HAI and systemic 5FU did not improve survival compared with systemic fluorinated pyrimidine.[24] Further studies are needed to evaluate the effect of HAI and systemic chemotherapies in combination.

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