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CASE REPORT

Alpha-fetoprotein-producing colon cancer with atypical bulky lymph node metastasis

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Abstract

Alpha-fetoprotein (AFP)-producing colorectal cancer is extremely rarely reported until now. All of the reported cases harboring synchronous hematogenous spread including liver and/or lung metastasis had a poor prognosis and died within 12 mo. We here describe a 71-year old man with AFP-producing colon cancer who presented with an unusual bulky lymph node metastasis instead of hematogenous spread. He underwent adjuvant chemotherapy in addition to curative surgical resection, which prolonged his survival.

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Key words: Alpha-fetoprotein; Colon cancer; Bulky lymph node metastasis; Computed tomography; Colonoscopy

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INTRODUCTION

Alpha-fetoprotein (AFP)-producing colorectal cancer is extremely rare, and only ten cases have been described in the English literature[1]. All reported cases presented with lung and/or liver metastasis and had a very poor prognosis. We here report the first case of AFP-producing colon cancer with bulky lymph node metastasis. This patient had characteristics such as harboring synchronous bulky nodal involvement but not hematogenous spread. Interestingly, he could be curatively operated and survived a long time after adjuvant chemotherapy in addition to surgical resection.

CASE REPORT

A 71-year old man visited our hospital for positive fecal occult blood and mild anemia. Physical examination disclosed a painless abdominal mass, approximately 50 mm in diameter, in the right lower quadrant of abdomen. Colonoscopy revealed an ulcerative lesion suggestive of an advanced colon cancer in the cecum (Figure 1). Biopsy specimens revealed a moderately-differentiated adenocarcinoma. Additionally, preoperative computed tomography of the abdomen and pelvis showed a bulky mass around the cecal cancer, which suggested nodal involvement corresponding to the palpated abdominal mass on physical examination (Figure 2). However, no distant hematogenous spread, including liver or lung metastasis, was detected. The serum AFP level was high (318.9 μg/L before operation). Right hemicolectomy including lymph node dissection was performed uneventfully, and histological examination of the surgical specimen revealed a subserosally invasive poorly-differentiated adenocarcinoma with nodal involvement. Immunohistochemically, both the primary tumor and the bulky lymph node metastasis showed strong expression of AFP. The serum AFP level became normal after adjuvant chemotherapy in addition to surgery. The patient was in good condition at the time of our report and had no sign of recurrence in the past 5 years.

DISCUSSION

Elevated levels of AFP, commonly associated with hepatocellular carcinoma or embryonic cell carcinoma, have been reported in neoplasms of several other organs, such as pancreas, gallbladder and gastrointestinal tract. However, AFP-producing colorectal carcinomas are extremely rare. The reported colorectal carcinomas have generally occurred in middle-aged to older men with the

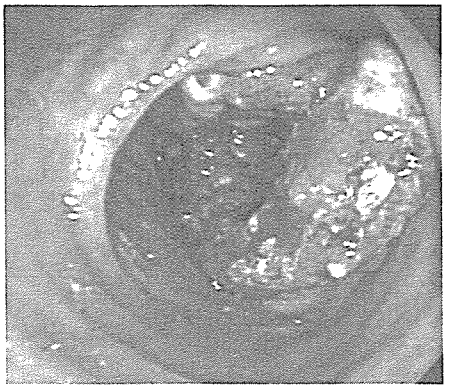

Figure 1 Colonoscopy showing a circumferentially advanced colon cancer in the cecum.

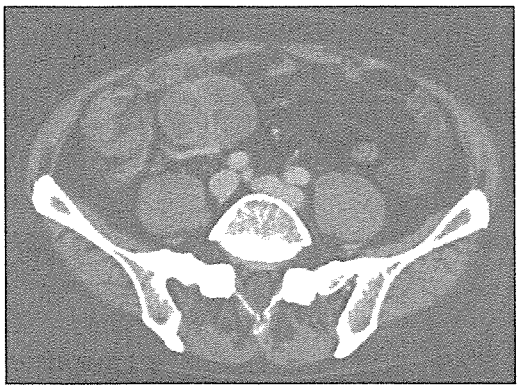

Figure 2 Abdominal computed tomography showing a bulky mass approximately 50 mm in diameter, suggestive of nodal involvement around the primary cecal cancer.

rectum most commonly affected, the serum AFP level is usually as high as several-thousand nanograms per milliliter[1-5]. Moreover, AFP appears to be a potential marker for tumor activity, as the serum level of AFP is higher in patients with liver metastasis than in those without liver metastasis[6]. AFP-producing colorectal carcinoma generally has a poor prognosis because of the frequent occurrence of blood-borne metastases. All the reported cases have extensive liver and/or lung metastases at the time of diagnosis and a very poor prognosis[1]. Our patient was unusual in comparison with the reported cases, as his AFP-producing colon cancer was located in the cecum, and showed only synchronous lymphogenous spread but not synchronous or metachronous blood-borne metastasis during a long time of follow-up. Furthermore, he was a long-time survivor, and was able to undergo curative surgical resection in addition to adjuvant chemotherapy. Clinical evaluation of a large number of patients is necessary to clarify whether systemic adjuvant chemotherapy is associated with a favorable prognosis for this kind of patients.

In summary, patients with AFP-producing colon cancer and synchronous bulky lymph node metastasis can survive a long time after adjuvant chemotherapy in addition to surgical resection.

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Importance of intra-individual variation in tumour volume of hepatic colorectal metastases

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Abstract

Aims: The efficacy of surgical resection for multiple colorectal hepatic metastases (MCHM) has been controversial. We examined the survival of patients who received surgery for MCHM and examined the factors associated with survival.
Methods: A retrospective analysis was performed of 50 consecutive patients who received hepatic resections for MCHM, defined as four or more metastatic lesions of colorectal cancer.
Results: Overall survival after hepatic resection for MCHM was 48% at 3 years and 43% at 5 years (median survival, 22.3 months). Multivariate analyses revealed that a coefficient of variation (CV) in volume of hepatic metastases in each individual patient above 1.8 ($P = 0.01$, HR = 4.08, 95% CI = 1.33–12.5) was the only poor prognostic factor after resection of MCHM.
Conclusions: A CV in volume of hepatic metastases in each individual patient above 1.8 predicts poor survival after hepatectomy of MCHM. Thus, the CV in volume of hepatic metastases in each individual patient might be useful in planning the therapeutic strategy for patients with MCHM.
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Keywords: Colorectal cancer; Hepatic metastases; Resection; Tumour volume; Coefficient of variation

Introduction

Hepatic resection is currently the only potentially curative treatment and the first-line therapy for colorectal hepatic metastasis.[1–5] The efficacy of hepatic resection has been reported for some cases of multiple colorectal hepatic metastases (MCHM); Bolton et al. reported that the survival of patients who underwent resection of more than four and/or bilobar hepatic metastases was equivalent to that of patients who underwent resection of fewer than four and unilobar hepatic metastases.[6] Nevertheless, hepatic resection for MCHM has been controversial because several reports demonstrated that having fewer lesions is a favorable prognostic factor after hepatic resection of colorectal hepatic metastases.[5,7–13]

Therefore, this study was conducted to evaluate the efficacy of resection for MCHM and elucidate any prognostic factors that could identify the patients who would benefit from surgical resection for MCHM. We focused on the histology of the tumour, tumour volume ratio (tumour volume/whole liver volume), and dispersion (coefficient of variation) of volume of hepatic metastases in each patient. We defined MCHM as four or more metastatic lesions of colorectal cancer of the liver, because four metastases corresponds to the limit of surgical resectability most widely used during the past decade.[6,14]

Patients and methods

Definition of MCHM

MCHM was defined as four or more metastatic lesions of colorectal cancer in the liver. Patients who showed any

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metastatic lesion outside the liver were excluded from the MCHM group. The diagnosis of MCHM was confirmed by diagnostic imaging before treatment.

Patient population

The records of 370 patients who had undergone hepatic resection for colorectal hepatic metastasis at the National Cancer Center Hospital East between September 1992 and August 2005 were examined retrospectively. Fifty of these patients met the criteria for MCHM. The patients consisted of 34 men and 16 women, ranging in age from 44 to 85 years, with a mean age of 60 years. Two of the patients had received oral uracil/tegafur and five had received 5-fluorouracil (5-FU)-leucovorin (LV) as adjuvant chemotherapy after primary colorectal resection. Few use of adjuvant chemotherapy after primary colorectal resections in our series ascribed to the fact that adjuvant chemotherapy has been rarely used after primary colorectal resections in our institution until 2002 although all patients with stage III colorectal cancer has received either 5-FU-LV or oral uracil/tegafur-LV since 2002.

The criteria for hepatectomy were as follows: metastatic lesions were confined to the liver and all lesions could be resected using oncologic principles (tumour-free margin and no residual disease) while preserving liver function. Basically, extended lobectomy plus partial resections was considered as the upper limit of hepatectomy that could be performed safely, and trisegmentectomy was applied only when the volume of the residual liver was deemed to be thoroughly abundant. Neither the number of metastatic tumours nor tumour size alone excluded patients from hepatectomy.

Irinotecan/5-FU/LV has been administered after hepatic resection of colorectal metastasis since 2003 when patients want to receive adjuvant chemotherapy; 9 patients in this study received the adjuvant therapy.

Operative procedure

After laparotomy, a careful search was performed for local recurrence, extrahepatic metastases, and peritoneal dissemination in the abdominal cavity. Any suspicious lesions were examined by biopsy. If metastasis in the regional lymph nodes (hepatoduodenal or peripancreatic lymph nodes) was suspected by preoperative imaging diagnosis or intraoperative findings, dissection of the regional lymph nodes was performed. Intraoperative bimanual liver palpation and ultrasonography were performed to confirm tumour location and size of the lesions in all patients, and all of the resections were ultrasound-guided procedures. Hepatic resection was performed with tumour-free resection margins by the forceps fracture method under inflow occlusion (Pringle's maneuver). Blood loss and operative time were recorded.

Clinical follow-up

After hepatic resection, patients were closely followed up with diagnostic imaging [chest X-ray and abdominal computed tomography (CT)] every 3 months, measurement of serum carcinoembryonic antigen (CEA) levels every month, and an annual colonoscopy to detect any tumour recurrence. The median follow-up duration of survivors was 27 months.

Measurement of tumour volume

Tumour volumes were obtained from helical CT scans of the abdomen, which were performed in all patients before initial treatment using 5-mm collimation after administration of 120 cc of non-ionic intravenous contrast injected at 2 cc per second with a 60-s delay. Images were reconstructed at 5-mm intervals using a standard soft-tissue algorithm.

Metastatic lesions and the whole liver were outlined manually on each axial slice using a computer mouse. The volume of metastatic lesions and that of whole liver were calculated automatically by multiplying the sum of the areas from each slice by the reconstruction interval. Then, tumour volume ratio was calculated (volume of tumour/volume of whole liver × 100%). All measurements were made by one radiologist.

For statistical analysis of inter-tumour variability in volume, in other words, dissimilarity in volume of metastases in each single patient, the coefficient of variation (CV; SD of the mean divided by the mean) was calculated for each case.

Histological parameters

The resected colorectal specimens and hepatic specimens were fixed in 10% phosphate-buffered formalin and cut at intervals of 5 mm and 10 mm, respectively, and then embedded in paraffin. Serial sections of 3-μm thickness were stained with hematoxylin and eosin (H&E) for morphological examination. Each case was histologically classified according to the histological type, tumour size, location, number of metastases, presence of serosal invasion, nodal status, and margin status. Histological diagnosis was performed according to the World Health Organization intestinal tumour classification.[15]

Statistical analysis

Analyses of survival were performed using the Kaplan–Meier method[16] and differences between the curves were tested using the log-rank test. The log rank test was also used to examine the significance of associations between survival curves and the following: CEA cutoff values 10 ng/ml, 20 ng/ml, 30 ng/ml, 50 ng/ml, 70 ng/ml, 100 ng/ml, and 200 ng/ml; tumour volume ratio cutoff values

1%, 3%, 5%, 8%, 10%, and 20%; and CV in tumour volume cutoff values 1.2, 1.4, 1.6, 1.8, and 2.0. Factors related to survival were analyzed with the Cox proportional hazards regression model.[17] A P value of less than 0.05 was considered to denote significance.

Results

Clinicopathological features of patients with MCHM

Fifty patients underwent resection of MCHM at the National Cancer Center Hospital East. Table 1 summarizes the primary and metastatic tumour characteristics. Four liver tumours were found in 20 patients, 5 tumours in 12, 6 tumours in 8, 7 and 8 tumours in 3 each, 9 tumours in 2, and 10 and 11 tumours in 1 each. Neither hepatoduodenal nor peripancreatic lymph node metastasis was found in any patient.

Surgical resections

Multiple partial resections were performed on 24 patients, segmentectomy on 12, lobectomy on 10, extended lobectomy on 2, and central bi-segmentectomy on 2 according to Couinaud's anatomical classification.[18] Forty-two of the 50 patients underwent multi-site resections. Microscopically positive surgical margins were observed in 11 patients. There was no perioperative mortality. Eleven complications were observed: five cases of biliary leak, two cases of intra-abdominal abscess, two cases of anastomotic leak in patients with synchronous metastases, one case of postoperative bleeding, and one case of liver failure.

Table 1
Clinicopathological findings of 50 patients with multiple colorectal hepatic metastases

	No. of patients
Primary colorectal tumour	
Stage (TNM classification)	
I	2
II	8
III	14
IV	26
Location	
Rectum	19
Colon	31
Maximum size of tumour (mean ± SD, cm)	4.9 ± 1.9
Histological type of adenocarcinoma	
Well or moderately differentiated	46
Poorly differentiated and others	4
Hepatic metastases	
Maximum size of tumour (mean ± SD, cm)	3.7 ± 2.3
Number of tumours (mean ± SD)	5.4 ± 1.8
Preoperative CEA level (mean ± SD, ng/ml)	65.4 ± 142.2
Synchronous/Metachronous	
Synchronous	24
Metachronous	26
Distribution of metastases	
Unilobar	12
Bilobar	38
Sum of the tumour volume (mean ± SD, cm^3)	61.2 ± 86.4
Tumour volume ratio* (mean ± SD, %)	4.8 ± 6.3
Coefficient of variation† in tumour volume (mean ± SD)	1.2 ± 0.6
Interval between resection of primary site and resection of hepatic metastases (median, mo)	7.9

SD, standard deviation; CEA, carcinoembryonic antigen. *Sum of tumour volume/whole liver volume × 100%. †Standard deviation of the mean divided by the mean.

Recurrences after resection of MCHM

Among the 50 patients, 37 developed recurrences. Locations of recurrence were as follows: liver in 32 patients, lung in 8, lymph node in 4, local recurrence in 3, peritoneum in 2, and bone and ovary in 1 each. Ten patients underwent resection for hepatic recurrences, 2 underwent resection for pulmonary recurrences, and one underwent resection for both hepatic and pulmonary recurrences. Of the remaining 24 patients, 19 received systemic chemotherapy, 2 received hepatic arterial infusion, and 3 received optimal supportive care.

Overall survival

Kaplan–Meier curve for overall survival after resection of MCHM is shown in Fig. 1. Actuarial overall survival after resection of MCHM was 48% at 3 years and 43% at 5 years with a median survival of 22.3 months. Meanwhile, overall survival of the entire cohort of 370 patients was 58% at 3 years and 46% at 5 years with a median survival of 27.6 months.

Association between clinicopathological factors and overall survival

To find prognostic factors for survival after resection of MCHM, clinicopathological factors and overall survival

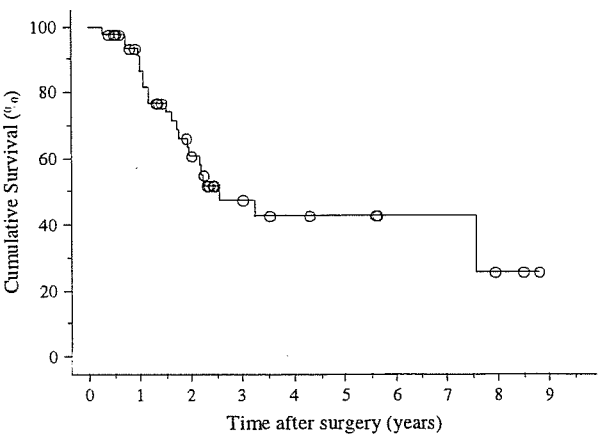

Figure 1. Cumulative survival curve for 50 patients with resected MCHM. The survival curve was generated by Kaplan–Meier analysis.

were analyzed in the 50 patients with MCHM (Table 2). Maximum tumour size above 5 cm ($P = 0.02$), CEA level before hepatectomy above 20 ng/ml ($P = 0.01$), tumour volume ratio above 8% ($P = 0.04$), and CV in tumour volume above 1.8 ($P < 0.01$) were significantly associated with poor overall survival.

We examined the independent predictive value of the aforementioned factors in overall survival. The data were analyzed using a Cox regression model (Table 3). Maximum size of the tumour was excluded from the analysis because it was strongly correlated with tumour volume. Then, only CV in tumour volume above 1.8 ($P = 0.01$; HR = 4.08; 95% CI, 1.33 to 12.5) had predictive value for decreased overall survival after resection of MCHM. Fig. 2 shows a case of MCHM with low CV (a) and another one with high CV (b) in tumour volume. The median survival of patients with CV in tumour volume below 1.8 was 25.0 months and that above 1.8 was 16.1 months (Fig. 3).

Table 2
Correlation between clinicopathological factors and overall survival after hepatectomy for multiple colorectal hepatic metastases

	No. of patients	Median survival (mo)	P
Primary colorectal lesion			
Location			
Colon	31	23.4	0.63
Rectum	19	18.5	
Stage (TNM classification)			
I, II	10	20.4	0.44
III, IV	40	22.7	
Lymph node metastasis			
Absent	18	23.4	0.82
Present	32	19.7	
Histological type of adenocarcinoma			
Well or moderately differentiated	46	23.5	0.08
Poorly differentiated and others	4	12.5	
Hepatic metastases			
Number of tumours			
<5	20	21.1	0.61
≥5	30	23.4	
Maximum size of the tumour (cm)			
<5	40	23.5	0.02
≥5	10	15.9	
Distribution of metastases			
Unilobar	12	21.1	0.60
Bilobar	38	23.4	
Microscopic surgical margin			
Negative	39	23.4	0.95
Positive	11	21.3	
CEA level before treatment (ng/ml)			
<20	27	24.6	0.01
≥20	23	17.5	
Tumour volume ratio* (%)			
<8	41	23.4	0.04
≥8	9	17.5	
Coefficient of variation† in tumour volume			
<1.8	42	25.0	<0.01
≥1.8	8	16.1	
Synchronous/Metachronous			
Synchronous	24	24.4	0.80
Metachronous	26	18.0	
Interval between colorectal resection and hepatectomy			
<1 year	39	24.6	0.91
≥1 year	11	12.1	
Adjuvant chemotherapy after hepatectomy			
Absent	41	23.5	0.61
Present	9	16.4	

CEA, carcinoembryonic antigen. *Sum of tumour volume/whole liver volume × 100%. †Standard deviation of the mean divided by the mean.

Table 3
Multivariate analyses of factors affecting overall survival after hepatectomy for multiple colorectal hepatic metastases

	Hazard Ratio (95% C.I.)	P
Hepatic metastases		
CEA level before treatment (ng/ml)		
<20	reference	0.07
≥20	2.39 (0.93–6.16)	
Tumour volume ratio* (%)		
<8	reference	0.87
≥8	1.10 (0.36–3.39)	
Coefficient of variation† in tumour volume		
<1.8	reference	0.01
≥1.8	4.08 (1.33–12.5)	

C.I., confidence interval; CEA, carcinoembryonic antigen. *Sum of tumour volume/whole liver volume × 100%. †Standard deviation of the mean divided by the mean.

Discussion

Several reports have described the efficacy of resection for MCHM. Bolton et al. analyzed clinical outcomes of 165 patients who underwent hepatic resection for colorectal metastases, and evaluated its efficacy and safety for patients with more than four and/or bilobar hepatic metastases.[6] The prognosis for such patients was almost equal to that of patients with fewer than four and unilobar hepatic metastases. Weber et al. reported that the 5-year survival rate after hepatic resection for 155 patients with four or more metastases was 23%, and twelve 5-year survivors were observed.[19] Minagawa et al. similarly reported a 32% 5-year survival of patients with four or more tumours.[13] In the present study, overall survival after hepatic resection for MCHM was 48% at 3 years and 43% at 5 years. Our results reconfirm that hepatic resection is beneficial for some patients with MCHM of colorectal cancer.

We found that a CV in tumour volume of above 1.8 was the only independent poor prognostic factor after resection of MCHM. Dispersion of tumour volume for each tumour is variable among patients. However, no previous study has attempted to quantify the dispersion of tumour volume or to evaluate its prognostic significance in colorectal hepatic metastases, and then we studied the association between the dispersion of tumour volume, quantified by CV, and survival after hepatectomy. Coefficient of variation is a statistical measure of the dispersion of data. It represents the ratio of the standard deviation to the mean, and is a useful statistic for comparing the degree of deviation from one

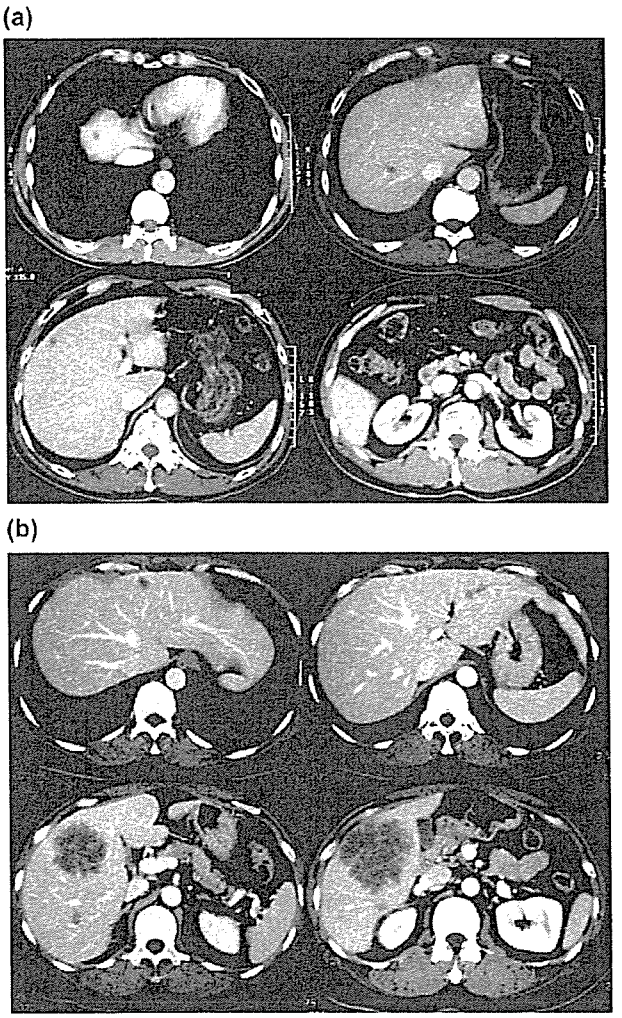

Figure 2. (a) A case of MCHM with low CV (=0.41) in tumour volume. (b) A case of MCHM with high CV (=3.20) in tumour volume.

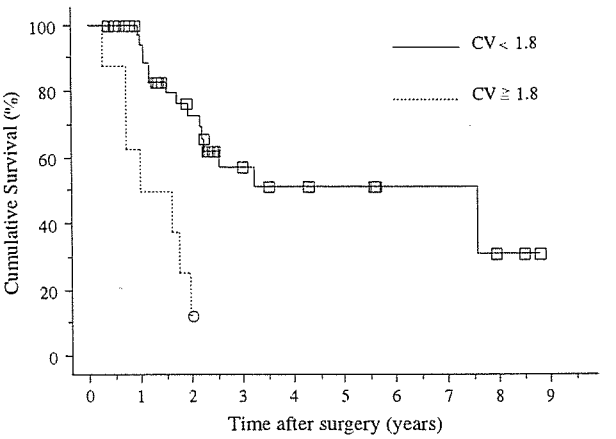

Figure 3. Cumulative survival curves after hepatic resection of MCHM according to CV in tumour volume. The median survival of patients with CV in tumour volume below 1.8 was 25.0 months and that above 1.8 was 16.1 months. Survival of patients with CV in tumour volume above 1.8 was poorer than that of patients with CV in tumour volume below 1.8 ($P < 0.01$).

data series to another, even if the means are drastically different from each other.[20,21] The mean tumour size varied widely among patients and CV was more useful than standard deviation in the present analyses.

The reason why high CV in tumour volume is strongly associated with independent poor prognosis after hepatic resection is obscure. However, a high CV may denote the coexistence of huge and tiny tumours. We propose two hypotheses to explain the association between high CV and poor prognosis. The first is that a high CV means the existence of a rapidly growing tumour; the high CV may result from the coexistence of tiny tumours growing at an ordinary rate and a huge tumour with an extremely aggressive nature and rapid growth. Another hypothesis is that high CV means a huge tumour with many intrahepatic metastases. Tiny tumours might have metastasized, not from the primary colorectal tumour, but from this huge hepatic tumour. Accordingly, a high CV might reflect progressive characteristics of MCHM.

In 8 patients with CV > 1.8, 6 suffered from severe hepatic recurrence after hepatic resection. In the remaining 2 patients, although lymph node recurrence was initially observed, hepatic recurrence with much tumour burden was recognized in the next few months. Then, severe hepatic recurrence could be a characteristic pattern of recurrence in patients with CV > 1.8. High CV might suggest extensive micro-metastases in the remnant liver.

Node-positive primary tumour,[4,22,23] serosal involvement of primary tumour,[22,23] stage of the primary tumour,[8,13] histological differentiation of primary tumour[22], a short disease-free interval from the primary tumour to metastasis,[4,11] extrahepatic disease at hepatectomy,[3,4,11,22,23] high CEA levels before hepatectomy,[4,5,8,10,22] large size of hepatic tumour,[4,8,23] the number of hepatic tumours,[4,5,8–13,22,23] bilobar distribution of hepatic tumour,[11] lymph node metastasis during hepatectomy,[3,11,13] an advanced age at hepatectomy,[8] and a positive margin of hepatectomy[4,5,8–11,22] have been reported as poor prognostic factors after resection of MCHM. However, the factors mentioned above were not found to be prognostic factors in this study. The difference between our results and those of other studies was partly due to difference of population. Patients of the present study consisted of only those with four or more metastatic lesions of colorectal cancer in the liver. Moreover, the difference might have resulted from the fact that CV in tumour volume, which had not been evaluated as a prognostic factor in other studies, affected patients' survival much more strongly than the aforementioned factors did in the present study.

In our study, the median survival of patients with CV in tumour volume above 1.8 was only 16 months and no 2-year survivors were found. Results of the present study lead us to conclude that hepatic resection is not

recommended as an initial treatment for MCHM when CV in tumour volume is above 1.8. Those patients should be treated by systemic chemotherapy and surgical resection then should be considered when the disease responds to the therapy.

Selecting the appropriate strategy according to the tumour staging has been an issue for patients with MCHM. Several studies proposed clinical risk scores incorporating the prognostic factors for predicting recurrence or prognosis after resection of MCHM to answer the clinical question.[4,8,11,23,24] However, those scoring systems and the factors consisting of each scoring system are not identical among the studies. The standard algorithm of treatment for MCHM is still obscure. Definitive and universal factors or a scoring system for predicting recurrence and prognosis after resection of MCHM is needed, and CV might be one of those factors in cases of MCHM.

The multistep process involving mutational events on both oncogenes and tumour suppressor genes is accepted for development of colorectal cancer, and several studies have shown that allelic imbalance correlated with staging and prognosis in colorectal cancer.[25,26] High CV might be caused by some genetic alterations. Genetic analysis such as evaluations of difference between the allelic imbalance of small tumours and that of large tumours in patients with high CV or evaluations of difference between the allelic imbalance of tumours in patients with low CV and that of tumours in patients with high CV may indicate particularly sensitive genomic regions and offer new information about the development of colorectal cancer. Further study is warranted to verify the prognostic significance of CV in tumour volume.

In conclusion, hepatic resections for MCHM sometimes contribute to long-term survival. Coefficient of variation in tumour volume above 1.8 might predict poor survival after hepatectomy of MCHM and be useful in planning the therapeutic strategy for patients with MCHM.

Acknowledgement

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Positron Emission Tomography with F-18 Fluorodeoxyglucose in Evaluating Colorectal Hepatic Metastasis Down-staged by Chemotherapy

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Abstract. *Background: The efficacy of positron emission tomography with ^{18}F fluoro-2-deoxy-D-glucose (FDG-PET) is obscure in evaluating viability or the extent of colorectal hepatic metastasis (CHM), down-staged by chemotherapy. Patients and Methods: A retrospective lesion-by-lesion analysis was performed for seven consecutive patients, who had received rescue hepatectomy for initially unresectable CHM, in order to evaluate the correlation between results of imaging modalities and the corresponding pathology. Results: The sensitivity and positive predictive value of the conventional modalities (CT and MRI) were 92% and 42%, respectively, while the sensitivity, specificity, positive predictive value and negative predictive value of FDG-PET were 58%, 100%, 100% and 75% respectively. The sensitivity of FDG-PET was 100% in evaluating the viability of tumors >2 cm, however, this fell to 17% in tumors <2 cm. Conclusion: FDG-PET is effective in assessing the viability of tumors >2 cm, but not those <2 cm, in patients with CHM down-staged by chemotherapy.*

Unresectable hepatic metastasis is one of the major obstacles in the treatment of colorectal cancer. Systemic chemotherapy for unresectable colorectal cancer has improved recently with the introduction of new effective agents (1-4). Even so, chemotherapy is rarely curative. Rescue hepatectomy after down-staging by chemotherapy is a potential treatment for unresectable colorectal hepatic metastasis (CHM) (5-8). However, pre-operative evaluation of tumor extent or viability is one of the issues in this strategy. The indication for rescue hepatectomy is based on the interpretation of the imaging of tumor extent or viability after down-staging by chemotherapy, however, evaluating the viability of hepatic tumors treated with chemotherapy is sometimes difficult by conventional imaging methods, such as computed tomography (CT) or magnetic resonance imaging (MRI), especially when the tumors have shrunk remarkably or exhibit notable calcification, after chemotherapy. Therefore, an effective diagnostic imaging modality to evaluate the viability of hepatic tumors after chemotherapy is needed.

Positron emission tomography with ^{18}F fluoro-2-deoxy-D-glucose (FDG-PET) is a functional imaging technique based on the increased utilization of glucose by tumor cells, and is effective for staging colorectal cancer (9, 10). Furthermore, the ability of FDG-PET to assess the pathological response to chemotherapy has been suggested in various malignant tumors (11-15). The correlation in CHM between FDG-PET findings and those of corresponding pathology has not been fully examined.

The present study was conducted to examine whether FDG-PET was able to assess tumor viability, before rescue surgery, for initially unresectable CHMs down-staged by chemotherapy and indicate which tumors should be resected.

Patients and Methods

Patient population. Seventy-four patients underwent hepatic resection for CHM at the National Cancer Center Hospital East, Japan, between January 2004 and July 2005, and 10 out of these underwent hepatic resection, after down-staging by chemotherapy. Since January 2004, all patients about to undergo rescue surgery are examined using FDG-PET pre-operatively, when informed consent is granted. Consequently, seven consecutive patients, who had been examined by CT, MRI and FDG-PET, were included in the present study. The patients were four men and three women, ranging from 44 to 70 years old. The location of the primary colorectal tumor was the colon in five patients and the rectum in two patients. All the

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primary tumors were well- or moderately-differentiated adenocarcinomas. The primary tumors were staged as II (n=2), III (n=2), and IV (n=3) according to the TNM classification.

Chemotherapy. The reasons for choosing chemotherapy instead of curative resection, initially, were multiple bilobar tumors in five patients, invasion to the bilateral bile ducts and portal veins in one and invasion to the 3 major hepatic veins in one. The chemotherapies performed for the unresectable tumors were 5-fluorouracil-leucovorin combined with irinotecan in four patients, 5-fluorouracil-leucovorin alone in one, oral uracil/tegafur in one and capecitabine in one. Five patients experienced a partial response and two patients had stable disease, based on the Response Evaluation Criteria in Solid Tumors.

Conventional imaging (CT, MRI). All patients underwent contrast-enhanced CT and MRI before hepatectomy. Multi slice CT with 16 DAS was used for this study (Aquillion, Toshiba Medical Sysytems, Japan). CT images were obtained using 5 mm collimation after administration of 100 ml of nonionic iodine intravenous contrast medium injected at 3 ml/sec with a 70-sec delay (portal-dominant phase). Images were reconstructed at 5 mm intervals using a standard soft-tissue algorithm.

MR images were aquired using a 1.5-T MR imager (Gyroscan Intera, Philips Medical Systems, Netherlands) with a phased array coil. A section thickness of 7 mm with a 1 mm gap was used for all sequences. T1-weighted fast field-echo image, T2-weighted fast spin-echo image and diffusion-weighted image with b factor 500 sec/mm^2 were performed. After gadodiamide injection, T1-weighted fast field-echo dynamic image were also obtained during the hepatic arterial, portal venous and delayed phases.

FDG-PET. Whole body FDG-PET was performed in five patients using a GE Advance Scanner (General Electric Medical System, Milwaukee, WI, USA), which has an axial field of view of 15 cm and a spatial resolution of 4.5 mm full-width-half-maximum. All patients fasted for at least 4 h prior to scanning. Sixty min after intravenous injection of 300 MBq of F18-FDG, emission scanning was performed in 5 min and transmission scanning in 1 min. Data acquisition was performed in 7 bed positions.

In the remaining two patients, PET/CT scanning was performed using a Discovery LS PET/CT system (General Electric Medical Systems, Waukesha, WI, USA) because our PET system had been replaced by PET/CT. The CT component was performed using a multi-detector scanner. The parameters were 140 kV, 80 Ma, 0.8 s/CT rotation, a pitch of 6, and a table speed of 22.5 mm/s. Scans were acquired from the skull base to mid-thigh level, in 7 bed positions, with a total acquisition time of 31.9 sec to 37 sec. CT data was resized from a 512x512 matrix to a 128x128 matrix to match the PET data, to allow for image fusion and generation of CT transmission maps. The PET data were also acquired in the same anatomic positions: in 7 bed positions at 5 min per position.

All PET studies were performed at least 4 weeks after completion of chemotherapy.

Rescue hepatectomy. At the National Cancer Center Hospital East, Japan, all lesions considered positive for malignancy, by any pre-operative diagnostic imaging evaluation, were resected by rescue hepatectomy. During this operation, all the tiny suspicious lesions that were definitive metastases before chemotherapy were resected.

In our patients, a careful search was performed after laparotomy for local recurrence, extrahepatic metastases and peritoneal dissemination in the abdominal cavity. Any suspicious lesions were examined by biopsy. Intra-operative bimanual liver palpation and ultrasonography were performed to confirm tumor location and size, in all seven patients and all of the resections were ultrasound-guided procedures. Hepatic resection was performed with tumor-free resection margins, by the forceps fracture method, under inflow occlusion (Pringle's maneuver). When small lesions that had been detected by pre-operative imaging could not be recognized by either palpation or intra-operative ultrasonography, the estimated part or segment of the liver occupied by the lesions was resected.

Extended lobectomy and multiple partial resections were performed on two patients each, and central bi-segmentectomy, lobectomy, and segmentectomy were performed on one patient each, according to Couinaud's anatomical classification.

Assessment of tumor viability with FDG-PET. In our hospital, when interpreting conventional CT and MRI findings, any hepatic lesions are classified according to the degree of confidence that a metastatic tumor is present, as follows: definitely present, probably present, possibly present, probably absent and definitely absent. Lesions that fall into the definitely present, probably present and possibly present categories are considered positive for malignancy, while lesions that fall into the other categories are considered negative. Lesions which are positive, by either CT or MRI, are considered positive by conventional examination.

In the present study, the category "possibly present" included the small lesions, detected using conventional imaging, that were used to indicate definitive metastasis, but which then could not be determined as viable or otherwise, due to a reduction in size or remarkable calcification after chemotherapy (Figure 1).

All lesions considered positive by conventional examination were compared with their corresponding pathology findings, as the standard reference and the sensitivity and positive predictive value were then calculated. Furthermore, these lesions were also assessed by FDG-PET according to the degree of confidence of malignancy, *i.e.* definitely present, probably present, possibly present, probably absent, and definitely absent. A discrete focus with increased FDG accumulation, markedly greater than that in the hepatic parenchyma, was interpreted as malignancy, being definitely present or probably present. Focally increased FDG uptake, minimally greater than in the liver, was considered possibly positive for malignancy, but heterogeneous uptake in the hepatic parenchyma without a focal lesion was considered to indicate that malignancy was probably absent. Lesions in the definitely present, probably present and possibly present categories were considered positive for malignancy, while those in the probably absent and definitely absent categories were considered negative.

FDG-PET findings were also compared with the pathology findings, as the reference, and then sensitivity, specificity, positive predictive value and negative predictive value were calculated according to tumor size: <2 cm and >2 cm.

Finally, the sensitivities, specificities, positive predictive values and negative predictive values were compared between the subgroups according to tumor size. The results of each imaging test were interpreted by at least two experienced radiologists.

Pathological examination. The resected hepatic specimens were fixed in 10% phosphate-buffered formalin, sliced at 5 mm intervals and embedded in paraffin. The findings of all lesions, considered positive

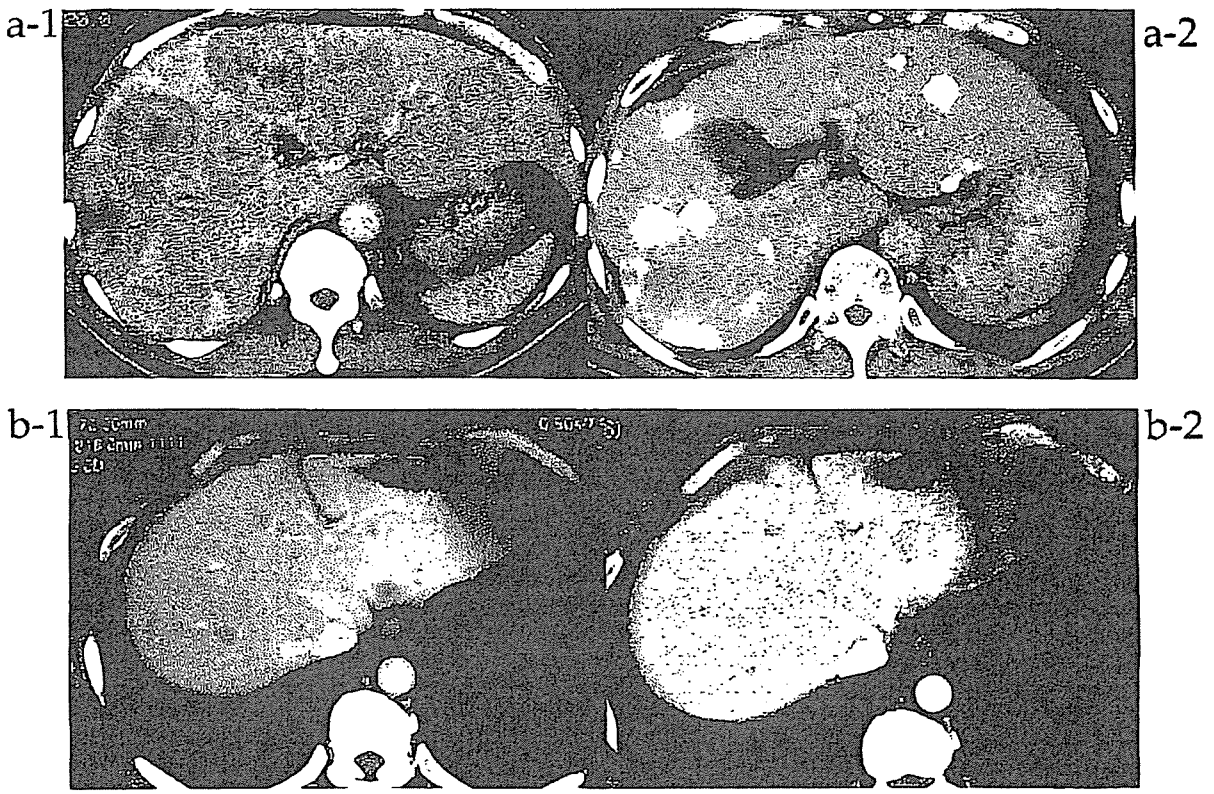

Figure 1. *a) A 45-year-old male with initially unresectable multiple colorectal hepatic metastases. (a-1) CT before chemotherapy. (a-2) CT after chemotherapy. Significant calcification was seen in the tumors. After rescue hepatectomy, histological examination revealed adenocarcinoma in most of the calcificated tumors. b) A 65-year-old female with multiple colorectal hepatic metastases. (b-1) CT before chemotherapy. (b-2) CT after chemotherapy. Tumors had reduced markedly in size.*

by any diagnostic imaging or intra-operative examination, were confirmed macroscopically and the lesions were then examined microscopically to evaluate viability. Serial sections 3 μm thick were stained with hematoxylin and eosin (H&E) for morphological examination. Histological diagnoses were based on the World Health Organization classification (16).

Statistical analysis. χ^2 analysis was used to assess sensitivity, specificity, positive predictive value and negative predictive value between subgroups according to tumor size. A *p*-value of less than 0.05 was considered to denote statistical significance.

Results

In the seven patients with CHMs down-staged by chemotherapy, 27 lesions were resected, all of which were considered positive for malignancy by pre-operative diagnostic imaging or intra-operative examination. Among the 27 lesions, 26 were deemed positive by at least one imaging modality, while the other could not be evaluated using imaging and was diagnosed by intra-operative examination. Twelve lesions were histologically diagnosed as adenocarcinoma, but no malignancies were demonstrated in the remaining 15 lesions.

Table I. *Comparisons of interpretations of CT, MR images and FDG-PET with pathology.*

	Pathological findings	
Imaging finding	Malignancy (12)	No malignancy (15)
CT and MR Imaging		
Positive (26)	11	15
Negative (1)	1	0
FDG-PET		
Positive (7)	7	0
Negative (20)	5	15

CT and MRI led to 26 lesions being diagnosed as malignant, while only 7 of these 26 lesions were considered positive by FDG-PET (Figure 2). No lesion was positive only by FDG-PET.

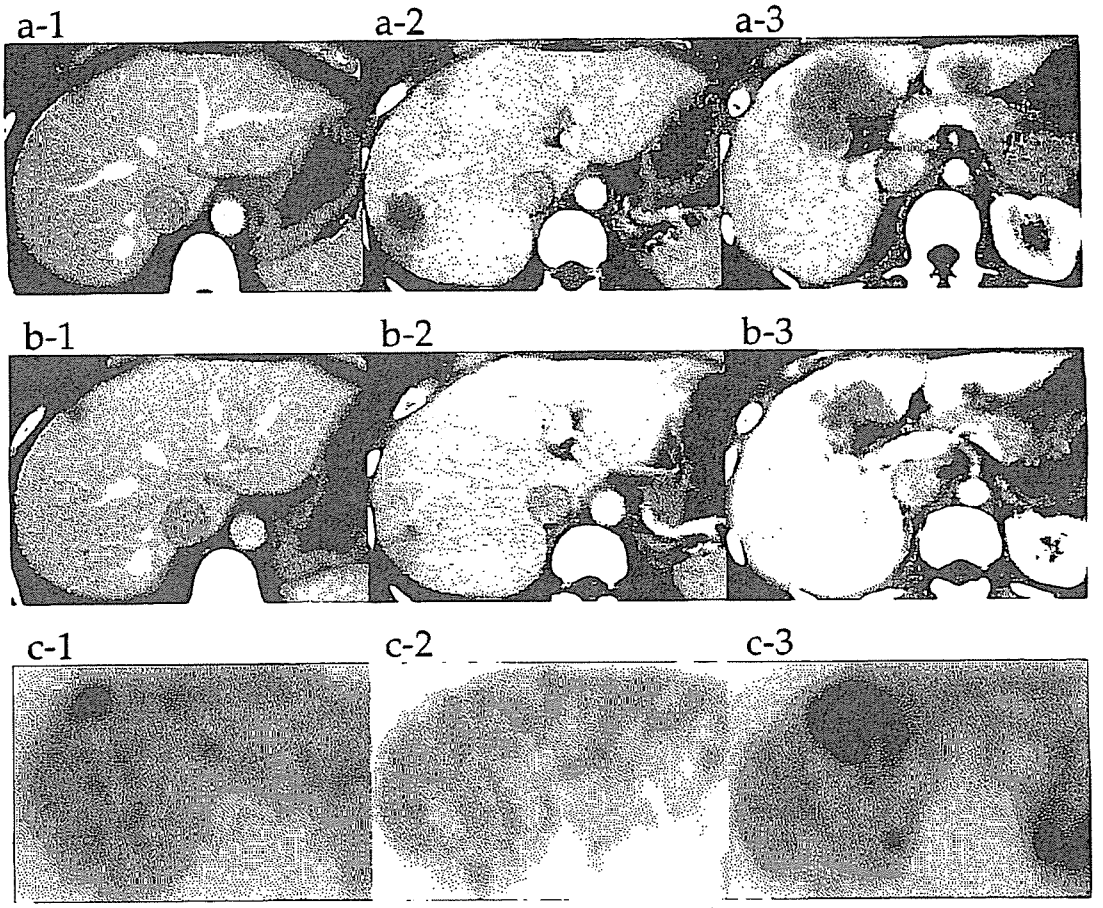

Figure 2. *A 44-year-old female with multiple colorectal hepatic metastases. (a-1, 2 and 3) CT before chemotherapy. Tumors were initially unresectable because of invasion to the hepatic hilum. (b-1, 2 and 3) CT after chemotherapy. Tumors in segments III, IV, V and VII showed significant reduction in size. (c-1, 2 and 3) FDG-PET after chemotherapy. By FDG-PET, tumors located in segments IV, V and VIII were considered positive, but tumors in segments III and VII were negative. Extended left lobectomy plus partial resections were performed. Tumors in segments III, IV, V and VIII proved histologically to be adenocarcinoma, but the tumor in segment VII had no viable cells.*

The interpretations of the conventional (CT/MRI) findings and FDG-PET findings were compared with the results of pathology in Table I. The sensitivity and positive predictive value of the conventional modalities were 92% (95% *CI*=0.73-1.00) and 42% (0.22-0.63), respectively, while the sensitivity, specificity, positive predictive value and negative predictive value of FDG-PET were 58% (95% *CI*=0.26-0.91), 100% (1.00-1.00), 100% (1.00-1.00) and 75% (0.54-0.96), respectively.

An assessment of the accuracy of conventional imaging and FDG-PET, according to tumor size (Table II), revealed that interpretation of the conventional findings and FDG-PET was highly accurate in lesions >2 cm. However, in lesions <2 cm, the positive predictive value for conventional imaging was only 26%, while the sensitivity for FDG-PET was only 17%, both of which were significantly lower than in lesions >2 cm. The specificity and negative predictive value of conventional imaging were not calculated, because lesions negative by both CT and MRI, were not resected, except for one which was diagnosed as positive by intra-operative examination. The viability of the 27 tumors could not be determined by any cut-off value of tumor-size (data not shown).

Discussion

We assessed the efficacy of FDG-PET in evaluating the tumor viability of CHM down-staged by chemotherapy, before rescue surgery. Our results indicate that FDG-PET is only effective in assessing the viability of hepatic lesions >2 cm after chemotherapy.

Table II. *Accuracies of CT, MRI, and FDG-PET in evaluation of tumor viability according to tumor size.*

	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	*P-value*
CT, MRI tumor size					
<2 cm	83 (5/6; 0.41, 1.00)	–	26 (5/19; 0.05, 0.48)*	–	<0.01*
≥2 cm	100 (6/6; 1.00, 1.00)	–	86 (6/7; 0.51, 1.00)*	–	
FDG-PET tumor size					
< 2 cm	17 (1/6; 0.00, 0.60)†	100 (14/14; 1.00, 1.00)	100 (1/1; –, –)	74 (14/19; 0.52, 0.96)	<0.01†
≥2 cm	100 (6/6; 1.00, 1.00)†	100 (1/1; 1.00, 1.00)	100 (6/6; 1.00, 1.00)	100 (1/1; –, –)	

Numbers in parentheses are the data used to determine the percentages and the 95% confidence intervals. *Difference between positive predictive value of CT and MRI in tumor <2 cm and that in tumor ≥2 cm. †Difference between sensitivity of FDG-PET in tumor <2 cm and that in tumor ≥2 cm.

The ability to use FDG-PET to assess the pathological tumor response to pre-operative chemotherapy, radiation or other treatment has been suggested in several tumors (11-15). In addition, correlation between decreased uptake in FDG-PET and histopathological response in the resected specimen was observed in patients, who underwent pre-operative chemotherapy or chemoradiotherapy for esophageal squamous cell carcinoma (17, 18), rectal cancer (19) and gastric carcinoma (20). However, the correlation between uptake in FDG-PET and the corresponding pathological findings has not been studied fully in CHM.

In the present study, portal phase helical CT and MRI were used as the conventional modalities. In our institution, diagnosis based on either, is routinely performed before hepatic resection for CHM, because portal phase helical CT has shown excellent sensitivity in detecting CHM and is considered as the standard pre-operative examination for CHM (21-23). Furthermore, SPIO-enhanced MRI and diffusion-weighted sensitivity encoding MRI have demonstrated high sensitivity equal to that of portal phase helical CT, and have excellent specificity in detecting CHM (24-26).

The present lesion-by-lesion analysis demonstrated that only 11 out of the 26 lesions that had pathological malignancy, considered positive for malignancy by conventional imaging. In the conventional examinations, the sensitivity of 92% for detecting hepatic viable CHMs was similar to that in the aforementioned studies, but the positive predictive value in tumors <2 cm was only 26%. Thus, CT and MRI were able to detect even small tumors, but could hardly evaluate the viability of small tumors after down-staging by chemotherapy.

On the other hand, FDG-PET showed excellent specificity (100%) and positive predictive value (100%), irrespective of tumor size. In tumors >2 cm, the sensitivity and negative predictive value for FDG-PET were both 100%. However, in tumors <2 cm, sensitivity was extremely low (17%). Thus, many of the tumors that shrunk to <2 cm by chemotherapy were undetectable by FDG-PET.

The reasons for this low sensitivity of FDG-PET in tumors <2 cm may be low spatial resolution, the partial volume effect and decreased FDG uptake in tumor tissue, after chemotherapy. Several groups reported that the sensitivity of FDG-PET for CHM was related to tumor size (27, 28). Lower sensitivity to smaller tumors was shown to be caused by the relatively low spatial resolution of FDG-PET and decreased measured activity concentration owing to the partial volume effect (29, 30). The partial volume effect reduces the measured activity concentration to a greater extent in smaller tumors.

Low sensitivity in FDG-PET has also been ascribed to the effects of chemotherapy itself. Chemotherapy may alter FDG uptake in two ways. First, the chemotherapy may reduce FDG uptake, by causing functional changes in tumor glucose metabolism. Spaepen *et al.* demonstrated that changes in tumor glucose metabolism occured rapidly after chemotherapy, as demonstrated using transplants of Daudi cells in SCID mice (31). Second, a decrease in viable cells by necrosis or apoptosis induced by chemotherapy may diminish FDG uptake in the tumor. Swisher *et al.* studied the correlation between the percentage of residual tumor and standardized uptake value (SUV) of FDG-PET after pre-operative chemoradiation in patients with esophageal cancer (18). They found that patients with >50% histological tumor viability had a significantly higher average SUV compared with those with <50% histological tumor viability. However, the SUV of tumors with no viability was similar to that of tumors with 10-50% tumor viability. Accordingly, when chemotherapy shows excellent efficacy in CHMs, it is extremely difficult to detect the resulting low FDG uptake by PET.

Our results suggest that the viability of small tumors that have been down-staged by chemotherapy can hardly be evaluated by CT, MRI or FDG-PET. Thus, at the moment, lesions considered positive by either CT or MRI should be treated by surgical resection in order to avoid leaving viable metastases in the residual liver. When surgical resection is not suitable for the specific lesion, perhaps due the small amount of residual liver, locoregional therapy, such as radiofrequency ablation or cryosurgery may become the preferred treatment options (6, 7).

The present study has nevertheless some limitations. The number of subjects in our study was relatively small, although the results have significant implications for rescue surgery for CHMs after chemotherapy. Furthermore, only two of the seven patients underwent PET/CT. The recent introduction of combined FDG-PET and CT has improved imaging accuracy by allowing accurate anatomical localization of FDG uptake. The sensitivity of PET/CT may be superior to that of FDG-PET for the detection of viable CHMs after chemotherapy. However, a major improvement in sensitivity is not expected, because the fundamental problem of detecting small viable tumors in PET is not resolved even using PET/CT.

New functional imaging with higher sensitivity for detecting small viable tumors is necessary to improve rescue surgery for CHM.

FDG-PET can be used to accurately assess the viability of CHMs >2 cm, before rescue surgery for initially unresectable CHMs down-staged by chemotherapy, but cannot be used for hepatic tumors <2 cm, because of the extremely low sensitivity of FDG-PET for such tumors.

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Laparoscopic Sentinel Node Mapping for Colorectal Cancer Using Infrared Ray Laparoscopy

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Abstract. *Background: Sentinel lymph node (SN) mapping by dye injection on conventional laparoscopy (CL) is often precluded by the presence of mesenteric adipose tissue in patients with colorectal cancer. SN mapping on CL was compared with that on infrared ray laparoscopy (IRL) during laparoscopy-assisted colectomy (LAC). Patients and Methods: Forty-eight patients with colorectal cancer who underwent LAC were enrolled. The tumor was identified by intra-operative fluoroscopy with marking clips. The tumor was stained intra-operatively by peritumoral injection of indocyanine green dye. SNs were observed by CL and by IRL. Results: In all 48 patients, dye injection and tumor localization during LAC were successful. The identification of SNs on IRL was approximately five times better than that on CL. There were no false-negative cases in T1 and T2 disease by IRL. Conclusion: SN mapping on IRL is superior to that on CL. SN mapping by IRL might be feasible for T1 and T2 tumors.*

Sentinel node (SN) navigation is a new technology that has been clinically validated and used to evaluate malignant melanoma (1) and breast cancer (2). SNs are the lymph nodes that first receive drainage from a tumor and, therefore, have the highest likelihood of containing metastases. Whether SN navigation can optimize surgery for colorectal cancer (CRC) remains controversial, but SN mapping has been found to be diagnostically useful in patients with early CRC (3). Wood *et al.* (4) reported that the intra-operative peritumoral injection of blue dye consistently identified SNs during laparoscopy-assisted colectomy (LAC). SNs were mapped by the submucosal injection of dye on intra-operative colonoscopy, or by the use of a spinal needle and percutaneous subserosal injection of dye at a premarked site (pre-operative tattooing of polypectomy site with carbon). However, our experience indicates that laparoscopic SN mapping by dye injection is technically difficult because injection of the dye into the colon wall during LAC is cumbersome. Submucosal injection of dye on intra-operative colonoscopy makes LAC difficult and problematic. Distension of the small intestine with air on colonoscopy interferes with the operative field and precludes laparoscopic procedures. Moreover, intra-operative colonoscopic examinations require considerable time, especially in patients with right-sided colon cancer. In contrast, percutaneous subserosal injection of dye into the thin colon wall is difficult and dye often leaks out of the colorectal wall (5, 6). Staining of SNs frequently cannot be accurately assessed in ordinary white light on conventional laparoscopy (CL) because of mesenteric adipose tissue. To solve these problems, infrared ray laparoscopy (IRL) (Olympus Corp., Tokyo, Japan) was used to map SNs during LAC in patients with CRC in whom saline was injected near the tumor before dye injection.

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Key Words: Sentinel node navigation, lymphatic mapping, infrared ray, colorectal cancer, laparoscopic colon resection.

Patients and Methods

Patients. Between July 2002 and December 2004, a total of 48 patients (28 women and 20 men; age range, 40-88 years; mean age, 63.9 years±12.6 [SD]; body mass index [BMI], 17-30; mean BMI, 22.5±2.9 [SD]) who underwent LAC for CRC or tumors *in situ* were enrolled. These patients were referred to our institution for treatment of CRC.

All patients had malignant polyps that were partially or completely removed during colonoscopy but required segmental colon resection, or large malignant tumors that could not be removed by colonoscopy. The tumor characteristics are shown in Table I. All the patients were specifically questioned about drug reactions and the absence of specific allergies was confirmed. Oral and written informed consent for LAC and SN mapping were obtained from all the patients before the procedures were performed.

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Table I. *Tumor characteristics and number of successful sentinel node mapping on infrared ray laparoscopy without false negative.*

	No. of patients	No. of successful mappings	*P*
Total no. of patients	48	42	
Tumor site			NS according to tumor site
Cecum	3	2 (67)	
Ascending colon	5	4 (80)	
Transverse colon	4	4 (100)	
Descending colon	1	1 (100)	
Sigmoid colon	24	22 (92)	
Upper rectum	11	9 (82)	
Tumor differentiation			NS according to tumor differentiation
Well	22	21 (95)	
Moderate	22	18 (82)	
Mucinous	4	3 (75)	
Depth of invasion			<0.0001, pT1-2 *vs.* pT3
pT1	25	25 (100)	
pT2	4	4 (100)	
pT3	19	13 (68)	
TNM stage[a]			<0.0001, stage I/II *vs.* III/IV
I	25	25 (100)	
II	12	11 (92)	
III	11	6 (55)	
IV	0	0	

NS = not significant; Values in parentheses are percentages. [a]Histopathological staging for lymph node metastasis according to standard hematoxylin and eosin staining. [a]TNM, tumor node metastasis.

Sentinel node mapping by IRL. Infrared rays have none of the undesirable effects of ultraviolet rays and only permeate tissue (7). Because infrared rays are absorbed by indocyanine green dye (ICG), lymph nodes and lymph vessels containing ICG can be visualized by infrared irradiation (8).

Examination techniques. Laparoscopic abdominal exploration was performed to rule out intra-abdominal metastasis. Intra-operative fluoroscopy was performed and the location of the tumor or polypectomy site was identified with marking clips set on pre-operative colonoscopy. Intra-operative colonoscopy was not performed in all patients. The location of the tumor was easily and accurately identified on laparoscopic images and fluoroscopic images at the same time. The involved segment of the colon was mobilized without disruption of the lymphatic vessels or blood vessels. ICG (25 mg) (Diagnogreen®; Dai-Ichi Pharmaceutical Co., Ltd., Tokyo, Japan) diluted with 5 ml of distilled water was used. First, 1 - 3 ml of saline was injected into the colon wall from the serosal side *via* a percutaneously inserted 25-G long needle to ensure correct placement of the needle into the colon wall, confirmed by mild resistance and bulging of the serosa. Then, the ICG solution was carefully injected just proximal and distal to the tumor, taking care not to puncture the tumor. The total amount of ICG solution injected was 5 ml, as described previously (9). After 5 min, green-enhanced SNs were observed on CL, and black-enhanced SNs were observed on IRL. Each SN had been marked with clips during laparoscopic surgery. Green-enhanced and black-enhanced SNs were confirmed by three surgeons. SN mapping added 20 - 25 min to the operating time. Mobilization of the colon was completed. The involved segment of the colon and the regional lymph nodes, including all black-enhanced SNs, were then extracorporeally resected *en bloc* through a minilaparotomy.

Table II. *Identification of sentinel nodes on conventional laparoscopy and on infrared ray laparoscopy in patients with colorectal cancer.*

	CL	IRL	*P*
Number with sentinel nodes	32	169	
Mean sentinel nodes/patient	0.68±0.86	3.5±1.7	<0.001
Range of sentinel nodes/patient	0-3	0-7	<0.001

CL = conventional laparoscopy; IRL = infrared ray laparoscopy.

The specimen was processed in a standard fashion and stained with hematoxylin and eosin (H&E). The primary neoplasm and all lymph nodes underwent routine microscopic analysis.

Statistical analysis. The relationships between successful SN mapping on IRL and tumor characteristics were assessed by χ^2 test (Table I). The Mann-Whitney *U*-test was used to analyze the difference between the identification of SNs by IRL and that by CL (Table II). Differences with *p* values of less than 0.05 were considered statistically significant.

Results

Feasibility. In mesenteric adipose tissue, lymph nodes and lymph vessels not seen in ordinary white light were visualized by IRL (Figure 1). When IRL was compared with white light in the same region and at the same time, IRL was found to provide much better visualization of the lymph nodes and lymph vessels. The identification of SNs on IRL was approximately five times better than that on CL (Table II). There were no complications specifically related to either method. No patient had to be reverted to open surgery because of uncontrollable bleeding or trauma.

Sentinel node detection and location. In all 48 patients, the dye injection and tumor localization during LAC were precise and successful. No tumors were punctured during the dye injection. Black-enhanced nodes were identified in 47 out of the 48 patients (97.9%). In the one failed case, where the black enhanced nodes were negative, the tumor was pT3 stage. Metastases were found in the lymph nodes

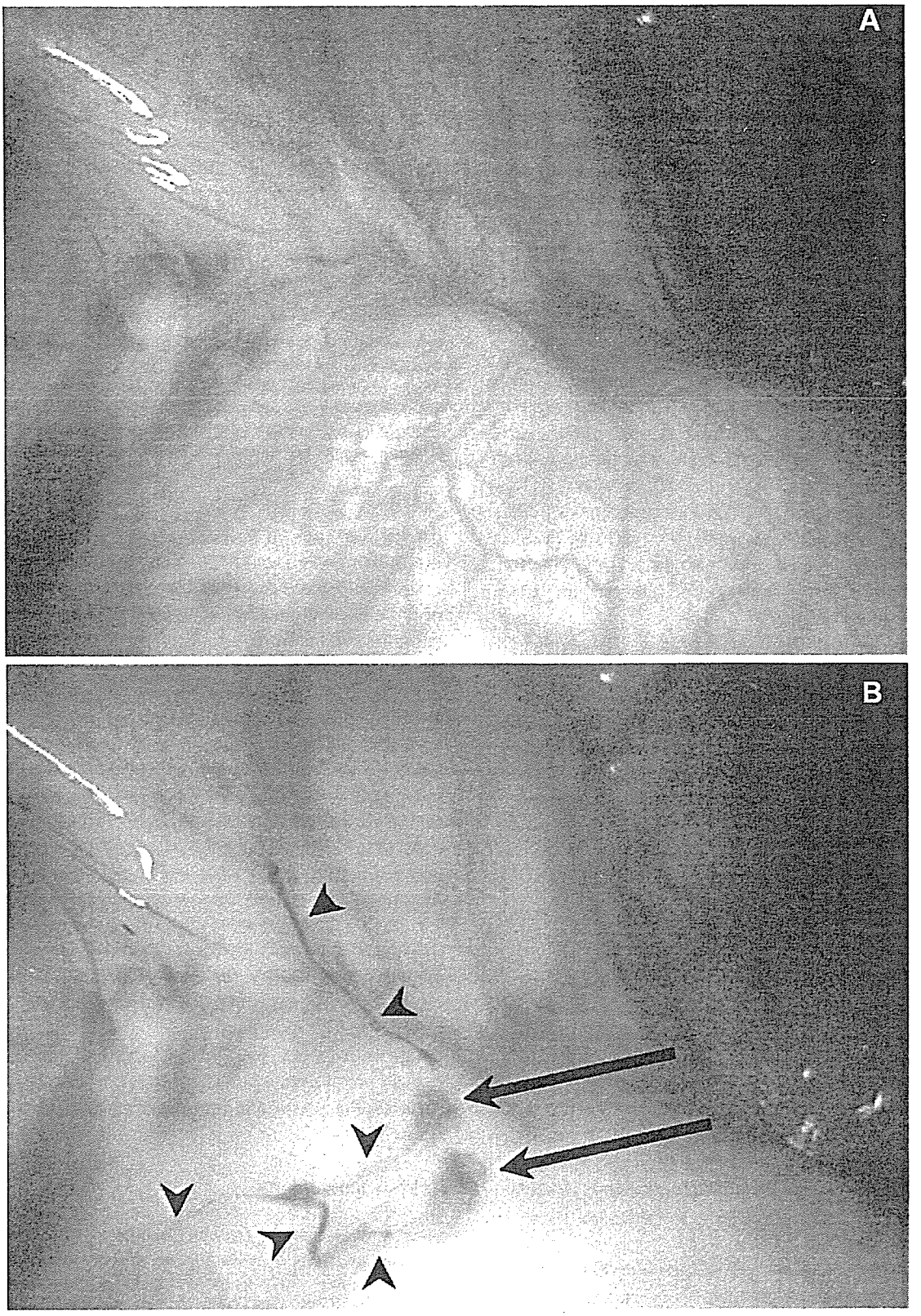

Figure 1. *Laparoscopic sentinel node mapping for the sigmoid colon. (A) Regional lymph nodes and lymph vessels cannot be observed by conventional laparoscopy. (B) Black-enhanced regional lymph nodes (arrows) are clearly visualized by infrared ray laparoscopy. The path of the black-enhanced lymph vessels (arrowheads) can be clearly followed at the same time.*