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Diseases of the Colon & Rectum

The Risk of Multiple Primary Malignancies with Colorectal Carcinoma

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PURPOSE: With advances in diagnostic techniques and treatment modalities, the number of patients identified with colorectal carcinoma who develop multiple primary malignancy during long-term follow-up has been increasing. We investigated multiple primary malignancies occurring in a large number of colorectal carcinoma patients who had undergone surgery in the 1980s at our institution. METHODS: A total of 1,304 Japanese patients with colorectal carcinoma treated between January 1980 and December 1989 were prospectively followed to investigate the situations in which multiple primary malignancies occurred. To determine whether the incidence of multiple primary malignancies in this series was higher than expected, we calculated the expected numbers of carcinoma occurrences and evaluated these findings by exact binomial test. RESULTS: The median follow-up period was 95 months. The incidence of multiple primary malignancy was 18.7 percent (143/765) among males and 14.7 percent (79/539) among females. The most common site of multiple primary malignancy among males was the stomach, followed by the lung, prostate, larynx, liver, esophagus, and urinary bladder. The most common site among females was the uterus, followed by the stomach, breast, and liver. The sites that showed a higher incidence of multiple primary malignancy than the expected value were: the prostate, larynx, urinary bladder, oral cavity/pharynx and thyroid among males, and the uterus and oral cavity/pharynx among females. CONCLUSIONS: Fifteen to 20 percent of Japanese colorectal carcinoma patients experienced multiple primary malignancies. Postoperative long-term screening methods should be established considering the actual occurrence numbers and risk rate of multiple primary malignancies in addition to metachronous colorectal carcinoma. [Key words: Colorectal carcinoma; Multiple primary malignancy; Follow-up; Expected numbers of carcinoma occurrences]

The incidence rates of each organ carcinoma vary with the times, racial or ethnical groups, and countries. In terms of age-adjusted incidence rates in Japan, a recent report showed that the most common carcinoma among males is gastric carcinoma, followed by colorectal carcinoma and lung carcinoma; and the most common carcinoma among females is colorectal carcinoma, followed by breast carcinoma and gastric carcinoma.[1] Among those carcinomas, the incidence of colorectal carcinoma is rising among both males and females. With advances in diagnostic techniques and treatment modalities, the outcomes of colorectal carcinoma treatment have improved, whereas the number of patients who develop multiple primary malignancy during long-term follow-up has simultaneously increased. However, with regard to the incidence of concurrent colorectal carcinoma and multiple primary malignancy in Japanese patients, many previous reports have merely indicated the number of concurrences, and few reports have described the incidence of the concurrences in relation to patient age and follow-up period.[2–5]

Taking patient age and follow-up period into consideration, we investigated the situations in which multiple primary malignancies occurred during long-term follow-up of a large number of colorectal carcinoma patients who had received treatment in the 1980s at our institution. This paper reports the findings of the investigation.

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PATIENTS AND METHODS

A total of 1,304 Japanese patients underwent colorectal carcinoma surgery at our institution between January 1980 and December 1989, and patient information and follow-up data were prospectively collected and added to the department database. In terms of follow-up, we routinely conducted periodic check-ups for the recurrence of colorectal carcinoma until the fifth postoperative year. No routine examinations were performed for multiple primary malignancies. Multiple primary malignancies were confirmed only when patients with multiple primary malignancies were diagnosed or treated at our institution, or documentation from other hospitals was obtained. The follow-up periods was defined as the interval between the date of surgery for colorectal carcinoma and the date at which information regarding the occurrence or absence of multiple primary malignancies was confirmed. We defined metachronous and synchronous carcinomas according to the criteria used by Warren and Gates[6]; synchronous carcinoma was defined as tumors detected after an interval of less than one year, and metachronous carcinoma was defined as tumors detected after an interval of one year or longer. Fifteen patients with familial adenomatous polyposis were excluded, but six patients with hereditary nonpolyposis colorectal carcinoma (HNPCC) were included in this study.

Statistical Analysis

To determine whether the incidence of multiple primary malignancies in this series was higher than the average incidence in Japan, we calculated the expected numbers of carcinoma occurrences by gender and tumor site for each of the following three periods: 1) from the date of birth to the date of surgery, 2) from the date of surgery to the final date of confirmation of survival, and 3) from the date of birth to the final date of confirmation; then we compared those expected numbers with the observed numbers.

The expected numbers of carcinoma incidences were computed by summing the cumulative risk of developing carcinoma for each patient during the period; those numbers were calculated based on the age-specific and gender-specific carcinoma incidence rates in Japan.[1,7] For example, the cumulative risk of stomach cancer from the date of surgery (1985) to the final date of confirmation of survival (1995) for a female patient aged 60 years at surgery was obtained by the sum of the incidence rates of stomach cancer for females aged 60 years in 1985, that for females aged 61 years in 1986, . . . , and that for females aged 70 years in 1995. In the case of a period of less than one year, the probability was obtained by multiplying the incidence rate by the number of days per 365.25. The methods of estimating cancer incidence in Japan and their limitations have been explained in previous reports, and corrections were applied to minimize any possible bias.[7–9] The cancer incidence rates after 2000 and before 1974 were assumed to be equal to those of 1999 and 1975, respectively, because data before 1974 and after 2000 have not been published. The two-tail P value was calculated exactly based on binomial distribution (exact binomial test).

Clinicopathologic parameters, such as gender, age, location of tumor, Dukes stage, and presence or absence of adjuvant treatment were compared by using Student's t-test or the chi-squared test where appropriate. $P < 0.05$ was considered significant.

RESULTS

Patient Characteristics

The follow-up periods for all patients ranged from 1 to 269 (median, 95) months. The mortality rate for male patients was 51.9 percent (397/765), and that for female patients was 41.7 percent (225/539). The patient demographics are summarized in Table 1. The incidence of multiple primary malignancy was 18.7 percent (143/765) among males and 14.7 percent (79/539) among females, showing no difference between the two groups ($P = 0.0614$). A comparison between patients with only colorectal carcinoma (O) and patients with multiple primary malignancies (M) demonstrated that the mean age at the onset of colorectal carcinoma was significantly higher in the M group among both males and females ($P < 0.0001$, $P = 0.0008$, respectively). With regard to the locations of colorectal carcinoma, the proportion of M was significantly higher among male colon carcinoma patients ($P = 0.0002$), but there was no difference among females ($P = 0.6277$). Patients with a more advanced Dukes stage had a significantly lower proportion of M in both males and females ($P < 0.0001$, $P = 0.0049$, respectively). With regard to adjuvant treatment, 37 patients underwent adjuvant radiotherapy and no patients developed subsequent

Table 1.
Characteristics of the Patients

Variable	Male (n = 765)		Female (n = 539)	
	Only Colorectal Carcinoma (n = 622)	Multiple Primary Malignancies (n = 143)	Only Colorectal Carcinoma (n = 460)	Multiple Primary Malignancies (n = 79)
Mean age at surgery for colorectal carcinoma (yr)	58.9[a]	65[a]	58.4[b]	63.2[b]
Synchronous		67.5		67.5
Metachronous–colorectal carcinoma preceding				
Age at colorectal carcinoma (yr)		61.2		59.4
Age at multiple primary malignancies (yr)		69.6		67.1
Metachronous–multiple primary malignancies preceding				
Age at multiple primary malignancies (yr)		58.1		53.5
Age at colorectal carcinoma (yr)		67.4		64.6
Location[g]				
Colon	272[c]	87[c]	229[d]	37[d]
Rectum	348[c]	55[c]	229[d]	42[d]
Dukes stage				
A	105[e]	41[e]	86[f]	17[f]
B	177[e]	49[e]	110[f]	31[f]
C	194[e]	33[e]	142[f]	22[f]
D	146[e]	20[e]	122[f]	9[f]

[a] $P < 0.0001$;
[b] $P = 0.0008$;
[c] $P = 0.0002$;
[d] $P = 0.6276$;
[e] $P < 0.0001$;
[f] $P = 0.0049$.
[g] Five patients with synchronous or metachronous carcinoma of the colon and rectum were excluded from the analysis.

Table 2.
Observed and Expected Number of Multiple Primary Malignancies in Males (n = 143)

Site	Total No. of Malignancies			Multiple Primary Malignancies Preceding and Synchronous			Colorectal Carcinoma Preceding		
	Obs	Exp	*P* Value	Obs	Exp	*P* Value	Obs	Exp	*P* Value
Stomach	59	54.7	0.5277	37	33.4	0.8596	22	20.9	0.7395
Lung	25	22.9	0.5957	13	10.2	0.0063	12	12.3	1
Prostate	12	5.5	0.0144	1	1.7	<0.001	11	3.6	0.0013
Larynx	11	2.1	<0.001	8	1.2	0.0066	3	1	0.0735
Liver	10	14	0.3441	3	6.9	0.2435	7	7	1
Esophagus	10	6.1	0.1468	5	3.2	0.0156	5	2.9	0.2198
Urinary bladder	10	4.9	0.0361	7	2.3	0.0283	3	2.6	0.7475
Oral cavity/pharynx	7	2.9	0.0274	4	1.6	0.0217	3	1.3	0.1412
Malignant lymphoma	5	3.7	0.4248	3	2.1	0.4786	2	1.5	0.6642
Kidney	4	2.8	0.372	2	1.3	0.0428	2	1.5	0.6643
Skin	4	1.7	0.093	4	0.9	0.5772	0	0.8	1
Pancreas	3	5.8	0.3958	1	2.9	0.7657	2	2.8	1
Thyroid	3	0.6	0.025	3	0.3	0.2849	0	0.3	1
Other	6			1			5		
Total	169			92			77		

Obs = observed; exp = expected.

Table 3.
Observed and Expected Number of Multiple Primary Malignancies in Females (n = 79)

Site	Total No. of Malignancies			Multiple Primary Malignancies Preceding and Synchronous			Colorectal Carcinoma Preceding		
	Obs	Exp	*P* Value	Obs	Exp	*P* Value	Obs	Exp	*P* Value
Uterus	26	8.1	<0.001	19	6.3	0.3079	7	1.8	0.0026
Stomach	18	17.1	0.8053	7	10.9	0.4458	11	6.1	0.061
Breast	14	9.4	0.1342	12	6.2	0.5413	2	3.1	0.7761
Liver	4	3.1	0.5618	0	1.4	0.0589	4	1.6	0.0845
Biliary tract	3	3.0	0.7744	1	1.3	0.1521	2	1.6	0.6755
Oral cavity/pharynx	3	0.7	0.0398	1	0.4	0.0617	2	0.3	0.0456
Malignant lymphoma	3	1.4	0.161	1	0.7	0.1713	2	0.6	0.1287
Skin	3	0.9	0.0628	1	0.4	0.0619	2	0.5	0.0842
Thyroid	3	1.4	0.1638	2	0.8	0.0434	1	0.6	0.4602
Lung	2	4.6	0.3431	1	2.1	0.7298	1	2.4	0.7397
Other	11			9			2		
Total	90			54			36		

Obs = observed; exp = expected.

malignancies. On the other hand, subsequent malignancies developed in 36 of 516 patients (7 percent) who received adjuvant chemotherapy and in 85 of 788 patients (10.8 percent) who did not receive adjuvant chemotherapy ($P = 0.0263$).

Multiple Primary Malignancies

The most common site of multiple primary malignancy among males was the stomach, followed by the lung, prostate, larynx, liver, esophagus, and urinary bladder (Table 2). In detail, the most common site of multiple primary malignancy in male colon carcinoma patients was the stomach (45 percent, 40/88) followed by the lung (14 percent, 12/88), whereas the incidences of stomach (35 percent, 19/55) and lung (23.4 percent, 13/55) carcinoma differed in male rectal carcinoma patients. The most common site among females was the uterus, followed by the stomach, breast, and liver (Table 3).

The sites that showed a higher incidence of multiple primary malignancy than the expected value were the prostate, larynx, urinary bladder, oral cavity/pharynx, and thyroid among males, and the uterus and oral cavity/pharynx among females. In particular, sites showing a significantly higher rate of malignancy than the expected value after colorectal carcinoma surgery were the prostate among males, and the uterus and oral cavity/pharynx among females.

With regard to uterine carcinoma, 14 cases had cervical carcinoma (12 cases of squamous-cell carcinoma and 2 cases of adenocarcinoma), 10 cases had corpus carcinoma (9 cases of adenocarcinoma and 1 case of adenosquamous carcinoma), and the details were unknown in 2 cases. The mean age at the onset of carcinoma was 55.3 (range, 33–76) years in cervical carcinoma cases, and 59.4 (range, 35–82) years in corpus carcinoma cases.

DISCUSSION

In Japan, the incidence of colorectal carcinoma has shown a tendency to increase in recent years, and as the treatment outcomes for each organ carcinoma have improved, it is not unusual to see patients with multiple malignancies involving the colorectum and other organs.[1,2] In the current series of Japanese colorectal carcinoma patients, multiple primary malignancy occurred in 18.7 percent of males, among whom the most common site was the stomach, and in 14.7 percent of females, among whom the most common site was the uterus. The organs in which multiple primary malignancies occurred in colorectal carcinoma patients at a higher incidence than the expected values were the prostate, larynx, urinary bladder, oral cavity/pharynx, and thyroid among males, and the uterus and oral cavity/pharynx among females, which were not necessarily correlated with the numbers of carcinoma occurrences. In previous studies, the reported incidence of other organ carcinomas among colorectal carcinoma patients in Japan ranged from 3 to 8.7 percent, but all of those studies used shorter follow-up periods than our study.[2–5] Our long-term follow-up demonstrated that 15 to 20 percent of Japanese colorectal carcinoma patients experience multiple primary malignancies.

In the results indicated above, there are some noteworthy observations. First, for gastric carcinoma, its incidence in Japan ranks high among both males and females, and also in our study, the occurrence of gastric carcinoma ranked high among both males and females,[1,10,11] but the number was almost the same as the expected value. Hence, it is conceivable that the high occurrence of gastric carcinoma in Japanese colorectal carcinoma patients is merely a reflection of the high incidence of gastric carcinoma in Japan. However, uterine carcinoma was the most common carcinoma among female patients, showing a significantly higher rate than the expected value. With regard to the occurrence of uterine carcinoma among Japanese females, a comparison between data from 1975 and data from 1998 shows that the age-standardized incidence of invasive cervical carcinoma decreased by approximately one-half from 13.4 to 7.2 per 100,000 females; conversely, the corpus carcinoma incidence increased from 1.4 to 4.5 per 100,000 females,[12] and in 1998, the ratio of invasive cervical carcinoma to corpus carcinoma was 1.6:1. In this study, these two carcinomas occurred to ratio of 14:10, and the inclusion of HNPCC cases did not result in a particularly high proportion of corpus carcinoma occurrence. The incidence of uterine carcinoma in Japanese females with colorectal carcinoma needs further investigation in the light of the increasing tendency of patients with corpus carcinoma.

An interesting point in this study is that, in male patients, the incidence of malignancies such as larynx, urinary bladder, and oral cavity/pharynx carcinomas, was significantly higher than the expected value. One of the background factors contributing to such a higher rate may be cigarette smoking. In Japan, adult males have a smoking rate of approximately 50 percent, compared with 20 to 30 percent in Western countries.[13] Recently it has been reported that smoking also is associated with colorectal polyp and colorectal carcinoma.[14–16] To determine whether colorectal carcinoma is a cigarette-associated malignancy and whether cigarette-associated malignancies are likely to occur frequently in colorectal carcinoma patients, it is necessary to conduct further study analyzing a large number of patients followed for a long period.

Regarding the occurrence of other organ carcinomas in colorectal carcinoma patients, the role of genetic factors that contribute to diseases, such as HNPCC, also should be investigated. The reported frequency of HNPCC accounts for up to 5 percent in Western countries, whereas in Japan the frequency ranges from 0.15 to 0.2 percent, which is a greatly low incidence.[17–20] This low rate will possibly rise in future long-term investigations, because the surveillance of patients with HNPCC has just begun in Japan.[19] The incidence of multiple primary malignancy has been reported to be high in patients with HNPCC.[18,21] In this study, we found ten cases of corpus carcinoma; however, as described above, the inclusion of HNPCC cases did not result in a particularly high proportion of corpus carcinoma. Similarly, we also found carcinoma of the renal pelvis in only one case among males, and carcinoma of the small intestine and ureter in only one case among females. It has been pointed out that gastric carcinoma also may occur frequently in patients with HNPCC, but as indicated above, it could be speculated that the high occurrence of gastric carcinoma in Japanese colorectal carcinoma patients is merely the result of the high gastric carcinoma incidence in Japan.[3,19]

In this study, patients with a more advanced Dukes stage had a significantly lower proportion of multiple primary malignancies in both males and females (Table 1). This can be explained by patients with a more advanced Dukes stage having a lower survival rate, resulting in shorter term follow-up and a lower proportion of multiple primary malignancies. However, patients with multiple primary malignancies demonstrated that the mean age at the onset of colorectal carcinoma was significantly high in both males and females compared with that in patients with single colorectal carcinoma. Although patients with single colorectal carcinoma are candidates for subsequent multiple primary malignancies with colorectal carcinoma, the reason for this result needs further investigation. Regarding the proportion of multiple primary malignancies, the proportion rate was significantly higher among male colon carcinoma patients than male rectal carcinoma patients. One possible reason for this is that HNPCC patients were included in this study. Obviously, the rates of colon carcinoma and multiple primary malignancies are elevated in HNPCC patients; however, there was no difference among females, although HNPCC patients also were included. The reason for the difference in incidence between male colon and rectal carcinoma patients needs further investigation.

Obviously, this study has some limitations. With regard to the effects of cigarette smoking, the patients in our series were not interviewed in detail

about their smoking history and we, therefore, could not accurately investigate the contribution of smoking to carcinogenesis in patients with colorectal carcinoma or in patients who developed multiple primary malignancy. In addition, no investigation into carcinoma occurrence in family members was performed during the long-term follow-up period, and hence we also could not obtain data regarding situations in which HNPCC and other hereditary colorectal carcinomas occurred. Moreover, the influence of adjuvant treatment on subsequent malignancies needs further investigation. In this study, no patient developed subsequent malignancies after radiotherapy. One possible reason for this is that patients who received radiotherapy were in a relatively advanced stage, and that only 9 of 37 patients who received radiotherapy survived for more than five years from the surgery for colorectal carcinoma. These points need to be improved in further studies.

CONCLUSIONS

This study was able to obtain some interesting findings on the incidence of other organ carcinomas in Japanese colorectal carcinoma patients. By conducting long-term follow-ups, we found that 15 to 20 percent of these patients in Japan develop multiple primary malignancies. This frequency is projected to rise in future studies with long-term follow-up. For colorectal carcinoma patients, postoperative long-term screening methods should be established, considering the actual occurrence numbers and the risk rate of multiple primary malignancies in addition to metachronous colorectal carcinoma.

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Second Hepatectomy for Recurrent Colorectal Liver Metastasis: Analysis of Preoperative Prognostic Factors

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Background: Second hepatectomy is a potentially curative treatment for patients with hepatic recurrence of colorectal cancer. However, there is still no consensus about the patient selection criteria for second hepatectomy under these circumstances, and the factors affecting prognosis after second hepatectomy remain uncertain.

Methods: Clinicopathologic data for 111 consecutive patients with colorectal liver metastasis who underwent second hepatectomy at a single institution between 1985 and 2004, and for whom complete clinicopathologic reports were available, were subjected to univariate and multivariate analyses.

Results: The morbidity and mortality rates were 14% and 0%, respectively, and the overall 5-year survival rate was 41%. Multivariate analysis revealed that synchronous resection for the first liver metastasis (hazard ratio, 1.8), more than three tumors at the second hepatectomy (1.9), and histopathological involvement of the hepatic vein and/or portal vein by the first liver metastasis (1.7) were independently associated with poor survival. We used these three risk factors to devise a preoperative model for predicting survival. The 5-year survival rates of patients without any risk factors, and with one, two, or three risk factors, were 62%, 38%, 19%, and 0%, respectively.

Conclusions: Second hepatectomy is beneficial for patients without any risk factors. Before second hepatectomy, chemotherapy should be considered for patients with any of these risk factors, especially with two or three factors, in the adjuvant or neoadjuvant setting to prolong survival. These results need to be confirmed and validated in another data set or future prospective trial according to the scoring scheme we outline.

Key Words: Second hepatectomy—Colorectal cancer—Liver metastasis—Prognostic factor—Neoadjuvant chemotherapy.

Hepatectomy is the best and most potentially curative treatment for patients with colorectal liver metastases, yielding a 5-year survival rate of 38% to 51%.[1–5] After a first hepatectomy, 60% to 70% of patients will develop recurrent disease, and one-third of these recurrences are limited to the liver.[6] The safety of hepatectomy has been increasing as a result of improvements in surgical techniques and perioperative management, and second liver resection has also been performed for patients with recurrent colorectal liver metastases. During the past decade, the reported outcomes of second hepatectomy have ranged from 21% to 49% in terms of 5-year survival after surgery. However, after second hepatectomy, some patients develop early recurrence in the liver,

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lung, and other organs, and in most of them, the disease is unresectable. Patients who experience recurrence within 6 months after second hepatectomy are already considered to have systemic disease before they undergo surgery. For such patients with systemic colorectal metastases, second hepatectomy is not beneficial and can even be harmful. However, the factors predicting early recurrence and poor outcome have not been established.

The purpose of this study was to find criteria that could be used to identify patients with recurrent liver metastases from colorectal cancer before surgery who would have a poor prognosis after second hepatectomy.

MATERIALS AND METHODS

Between October 1985 and November 2004, data for 111 consecutive patients with recurrent liver metastases from colorectal cancer who underwent first and second hepatectomies at the National Cancer Center Hospital, Tokyo, were collected and reviewed. Patients who did not undergo initial liver resection at our hospital were excluded from the study because we were unable to obtain enough clinicopathologic data for them.

We investigated 27 clinicopathologic variables pertaining to patient characteristics, clinical data, and histopathologic findings, such as sex, age, primary cancer location, lymph node status, timing of first hepatectomy, number of hepatic metastases, tumor diameter, tumor distribution, preoperative serum carcinoembryonic antigen level, extent of liver resection, surgical margin, venous invasion by liver metastases, and bile duct invasion. The extent of liver resection was defined according to the nomenclature; wedge, segmental, and bisegmental resections were classified as minor resection, and hemihepatectomy or more extended resections were classified as major resection. Patient outcomes were determined on the basis of clinical data obtained from the files as of August 2005. The median follow-up period for the 111 patients after second liver resection was 43 months (range, 1–207 months).

The prognostic significance of clinicopathologic factors in relation to survival was investigated by univariate and multivariate analyses. Data were censored in the analysis of overall survival if a patient was alive, and in the analysis of disease-free survival if a patient was alive without recurrent colorectal cancer. Survival rates were calculated by the Kaplan-Meier method and compared statistically by the log-rank test. Univariate comparisons of survival were performed by the log-rank test and multivariate analysis by the Cox regression model with the forward stepwise method (likelihood ratio). All variables were dichotomized for analysis. All statistical analyses were performed by SPSS for Windows, version 6.0 (SPSS-Japan Inc., Tokyo, Japan). All P values were two-sided, and differences at $P < .05$ were considered to be statistically significant.

RESULTS

Patient Characteristics and Follow-up

The 111 patients who underwent second hepatic resection with curative intent included 74 men and 37 women with a mean age of 59 years. The median interval between the first and second hepatic resections was 16 months (range, 4–96 months). At the last follow-up, 37 patients (34%) were alive with no evidence of recurrence, 12 (11%) were alive with disease, 61 (55%) had died of disease, and 1 patient was lost to follow-up. There were 23 actual 5-year survivors. The median follow-up time from primary resection was 69 months (range, 11–249 months), and the median follow-up from the second liver resection was 43 months (range, 1–207 months).

Clinical Features and Pathology

Primary Tumor

The site of the primary cancer was the colon in 75 patients (68%) and the rectum in 36 (32%). Histologically, there were 50 well-differentiated, 58 moderately differentiated, and 1 poorly differentiated adenocarcinoma, and 2 mutinous carcinomas. Metastatic lesions in the liver were found synchronously with the primary tumor in 58 patients (stage IV). Of the 53 patients with metachronous liver metastases, 13 patients had no lymph node metastasis (stage I or II), and 40 patients had lymph node metastasis (stage III).

First Liver Resection

Of the 53 patients with metachronous liver metastases, the median interval between the primary resection and the first hepatectomy was 16 months (range, 4–60 months), and 25 patients (47%) underwent the second hepatectomy within 12 months. Unilobar involvement was observed in 68 patients and bilobar involvement in 43. At the first hepatectomy, 43 patients had a solitary hepatic lesion, 67 had

Univariate Analysis of Survival

Factors Related to Primary Lesion

The results of univariate analysis of survival are listed in Table 1. The presence of metastatic lymph nodes was a significant predictor of worse outcome after second liver resection ($P = .03$). The location of the primary colorectal cancer and the histology of the primary lesion did not influence survival.

Factors Related to First Hepatectomy

Patients with metachronous liver metastases had a significantly better median survival time after second hepatectomy (60 vs. 32 months, $P = .009$). The patients who received blood transfusions during the first hepatectomy had significantly worse survival ($P = .049$). The number of tumors, size of the largest tumor, bilobar involvement, extent of hepatectomy, and serum carcinoembryonic antigen level were not prognostic factors. In terms of microscopic findings, invasions of the portal vein or hepatic vein, and a positive surgical margin tended to be associated with poor survival, but the difference was marginal ($P = .07$ and .07, respectively). Bile duct invasion was not a prognostic factor.

Factors Related to Second Hepatectomy

The 5-year survival was significantly better for patients with a disease-free interval of more than 6 months between the first hepatectomy and recurrence, as compared with patients with a disease-free interval of less than 6 months (49% vs. 22%, $P = .02$). Patients who had less than four nodules had significantly better survival than those with four or more (45% vs. 18%, $P = .001$). The size of the largest lesion at the second operation influenced survival, but not to a significant degree ($P = .09$). Similar to the first hepatectomy, patients who received blood transfusions showed significantly worse survival ($P = .03$), and bilobar involvement, extent of hepatectomy, and serum carcinoembryonic antigen level were not prognostic factors. Patients who had undergone resection of extrahepatic disease before second hepatectomy did not show worse survival. With respect to the microscopic features of the recurrent metastatic disease, a surgical margin, invasions of the portal vein or hepatic vein, and bile duct invasion had no statistically significant influence on survival.

Multivariate Analysis of Survival

Multivariate analysis identified three independent risk factors: synchronous first hepatectomy, four or

TABLE 1. *Univariate analysis related to survival*

Prognostic factor	No. of Patients	5-Year survival rate of second hepatectomy (%)	*P* value
Demographics			
Age			
< 60 y	56	43	.95
≥60 y	55	38	
Sex			
Male	74	38	.64
Female	27	46	
Primary lesion			
Location			
Colon	75	36	.17
Rectum	36	52	
Lymph nodes			
Negative	21	74	.03
Positive	90	33	
First hepatectomy			
Number of lesions			
< 4	90	43	.33
≥4	21	33	
Size			
< 5 cm	87	42	.45
≥5 cm	24	37	
Timing with primary			
Metachronous	53	51	.009
Synchronous	58	30	
Distribution			
Unilobar	68	44	.25
Bilobar	43	36	
Resection			
Minor	93	38	.92
Major	18	53	
CEA before first hepatectomy			
< 50 ng/dL	89	42	.31
≥50 ng/dL	22	37	
Blood loss			
< 1000 mL	91	35	.27
≥1000 mL	20	57	
Blood transfusion			
No	94	41	.049
Yes	17	35	
Surgical margin			
No	88	45	.07
Yes	23	29	
Vessel invasion			
No	89	46	.07
Yes	22	23	
Bile duct invasion			
No	72	36	.1
Yes	39	50	
Second hepatectomy			
Interval between first hepatectomy and recurrence			
< 6 mo	79	49	.02
≥6 mo	36	22	
Extrahepatic disease before second hepatectomy			
No	100	39	.31
Yes	11	54	
Number of lesions			
< 4	93	45	.001
≥4	18	18	
Size			
< 5 cm	100	44	.09
≥5 cm	11	16	

2 to 12 (median, 3) metastatic nodules, and one patient had more than 50 lesions. The median size of the largest hepatic lesion was 3.3 cm (range, 1.2–10 cm). Minor resection was performed in 93 patients and major resection in 18. The median blood loss was 698 mL (range, 50–3215 mL). Blood transfusion was performed in 17 patients. The surgical margin was negative in 89 patients and positive in 22. Invasions of the portal vein or hepatic vein by the liver metastases were found in 22 patients, and bile duct involvement was found in 39.

Second Liver Resection

The median interval between the first hepatectomy and detection of recurrence was 13 months (range, 2–92 months). Sixty-two patients had a solitary metastasis, and 49 had multiple metastases. The recurrent metastases ranged from 1.2 to 10 cm (median, 3.3 cm) in greatest dimension. Before second hepatectomy, pulmonary resection for lung metastasis was conducted in eight patients, and three patients underwent second hepatectomy and pulmonary resection simultaneously. After first hepatectomy, performed mostly in the 1980s, nine patients received adjuvant hepatic arterial infusion chemotherapy with 5-fluorouracil (5-FU), mitomycin C, and oral carmofur regimen,[7] and six patients received oral anticancer drugs for adjuvant therapy (carmofur in five patients, uracil-tegafur in one). Two patients who underwent colectomy plus simultaneous hepatectomy received adjuvant intravenous 5-FU plus leucovorin or mitomycin C, and one who had initially unresectable liver metastases was provided irinotecan for downstaging.

The second hepatectomy procedures included minor resection in 99 patients, hemihepatectomy in 6 patients, extended hemihepatectomy in 5, extended hemihepatectomy with bile duct reconstruction in 1, and central bisectionectomy in 1. Ninety-three patients had negative margins and 18 had positive margins. The median blood loss during the second liver resection was 913 mL (range, 95–4803 mL), and 22 patients received blood transfusions. No patient died during the perioperative course. Complications occurred in 16 patients (14%), including bile leakage in 8, abscess formation in 4, pleural effusion in 3, cholangitis in 1, and wound infection in 1. Invasions of the portal vein or hepatic vein were found in 25 patients, and bile duct involvement was found in 40.

Survival and Recurrence After Second Hepatectomy

Of the 111 patients who underwent second hepatectomy with curative intent, 61 had died by August 31, 2005. Overall 1-, 3-, and 5-year survival rates were

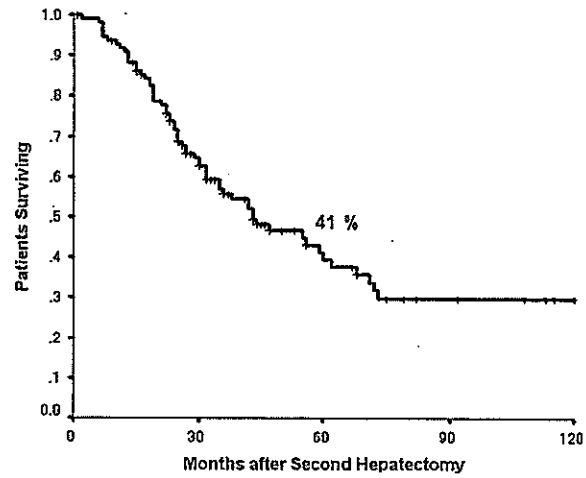

FIG. 1. Overall survival after second hepatectomy in patients with colorectal liver metastases.

91%, 74%, and 41%, respectively, from the time of second liver resection, with a median survival of 43 months (Fig. 1). There were 23 actual 5-year survivors. Recurrence after second hepatectomy occurred in 74 patients. Of these, 39 patients developed liver metastases (27 confined to the liver; 12 involving the liver plus other sites), and 37 developed lung metastases. Of them, 21 patients underwent surgery, including 13 third hepatectomies and 8 pulmonary resections. Twenty-seven patients experienced recurrence within 6 months after the second hepatectomy, and their median survival time was significantly worse than that of the others (15 vs. 60 months, $P = .0001$). Forty-four of the patients who experienced recurrence after second hepatectomy received chemotherapy for treatment. Hepatic arterial infusion chemotherapy was performed in seven patients who had isolated hepatic recurrence. 5-FU was given by infusion to 14 patients; seven received additional mitomycin C. Oral chemotherapy drugs were administered to 7 patients (uracil-tegafur plus leucovorin in 2, S-1 [tegafur/5-chloro-2,4-dihydroxypyridine/potassium oxonate] in 3, capecitabine in 1, and carmofur in 1), and intravenous 5-FU plus leucovorin was provided to 11. Twenty patients received irinotecan, eight received oxaliplatin, and one received bevacizumab. Irinotecan has been commonly used since 1999 in Japan, and most of the patients who experienced recurrence after 1999 benefited from irinotecan. The group that developed recurrence until 1998 (n = 19) had significantly worse survival than those after 1999 (n = 25) (median survival time, 23 months vs. 55 months, $P = .004$).

TABLE 1. *Continued*

Prognostic factor	No. of Patients	5-Year survival rate of second hepatectomy (%)	*P* value
Distribution			
Unilobar	68	45	.11
Bilobar	43	34	
Resection			
Minor	96	41	.67
Major	15	44	
CEA before second hepatectomy			
< 50 ng/dL	89	42	.31
> 50 ng/dL	22	37	
Blood loss			
< 1000 mL	73	40	.77
> 1000 mL	38	42	
Blood transfusion			
No	89	43	.03
Yes	22	29	
Surgical margin			
No	90	45	.16
Yes	21	22	
Vessel invasion			
No	75	36	.17
Yes	36	52	
Bile duct invasion			
No	71	43	.95
Yes	40	35	

TABLE 2. *Multivariate analysis with Cox proportional hazard model*

Prognostic factor	Relative risk	95% Confidence interval	*P* value
Synchronous timing of first hepatectomy	1.85	1.10–3.11	.02
Presence of vessel invasion at first hepatectomy	1.79	1.00–3.19	.049
Number of lesions at second hepatectomy ≥4	1.94	1.10–3.41	.022

more lesions at second hepatectomy, and invasion of the portal vein or hepatic vein at first hepatectomy (Table 2). Any of the variables related to microscopic findings—information that could only be obtained after the second hepatectomy—were not statistically significant prognostic factors.

All three risk factors identified in the multivariate analysis were based on information obtained before the second hepatectomy. Therefore, we tried to group patients according to risk factors. Thirty-four patients had no risk factors, 53 had one factor, 22 had two factors, and 2 had three factors. Survival expectancies at 5 years for patients with no risk factors, one or two risk factors, and three risk factors were 62%, 31%, and 0%, respectively, and these differences were statistically significant ($P = .001$) (Fig. 2). Two patients with three risk factors developed recurrence within 6 months and died at 15 months and 19 months, respectively, after the second hepatectomy.

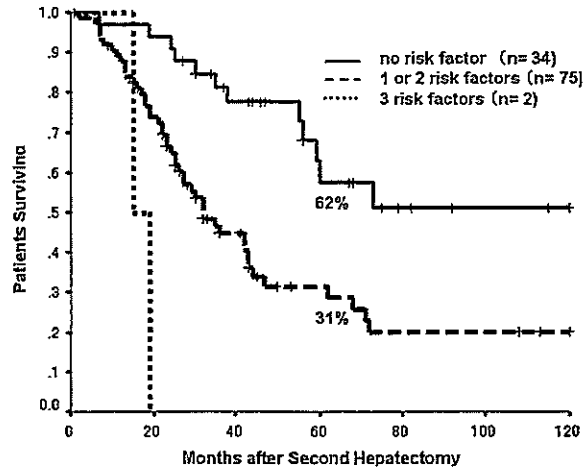

FIG. 2. Overall survival according to groups divided by number of risk factors identified in current study.

DISCUSSION

The only potentially curative treatment for patients with liver-isolated colorectal metastases is surgical resection. However, most cannot be considered candidates for surgery for reasons such as very large tumor, unfavorable tumor location, multinodularity, or inadequate hepatic reserve. Nevertheless, because of its impact on survival, surgical resection is the treatment of choice when it is feasible. Improvements in surgical techniques and perioperative management have made surgical resection more feasible, with a mortality rate of less than 3%.[2–4,8] For patients with recurrent colorectal liver metastases, second hepatic resection has been performed more frequently during the past decade.[6,9–22] The results of previous series involving more than 20 patients are listed in Table 3. Five-year survival rates of 38% to 51% have been reported for first hepatic resections,[1–5,23] and similar 5-year survival rates, ranging from 21% to 49%, can be achieved after second hepatic resection for well-selected patients. In fact, morbidity and mortality after second hepatic resection are almost comparable to those after initial hepatic resection. The median survival and 5-year survival rate in the present series were 43 months and 41%, respectively. Because conventional chemotherapy alone cannot achieve such favorable results, a second hepatectomy has become the treatment of choice for recurrent liver metastases from colorectal cancer.

TABLE 3. *Reports of second hepatectomy*

Author	Year	No. Patients	Mortality (%)	Morbidity (%)	5-Year survival	MST (mo)
Fong et al.[9]	1994	25	0	28	NR	30
Nordlinger et al.[10]	1994	116	.9	25	33[a]	NR
Que and Nagorney[11]	1994	21	5	NR	43[b]	41
Fernandez-Trigo et al.[12]	1995	170	NR	19	32	34
Riesener et al.[13]	1996	25	0	20	24[a]	NR
Adam et al.[6]	1997	64	0	20	26	46
Tuttle et al.[14]	1997	23	0	22	32	40
Yamamoto et al.[15]	1999	75	0	11	31	31
Muratore at al.[16]	2001	29	3.4	10	35[a]	NR
Suzuki et al.[17]	2001	26	0	33	32	31
Petrowsky et al.[18]	2002	126	1.6	28	34	37
Takahashi et al.[19]	2003	22	0	18	49[a]	23
Tanaka et al.[20]	2004	26	0	30	48[c]	NR
Sugawara et al.[21]	2005	27	0	22	49	41
Pessaux et al.[22]	2006	42	0	14	21	25

MST, median survival time; NR, not reported.
[a] Three-year survival.
[b] Four-year survival.
[c] Five-year disease-free survival.

Recently, systemic chemotherapy has led to marked improvements in median overall survival and progression-free survival.[24–26] These benefits are most pronounced with regimens containing irinotecan or oxaliplatin in combination with 5-FU plus leucovorin; median overall survival durations consistently approach 20 months, and some are as high as 24 months. Some patients experience early repeat recurrence within 6 months after second hepatectomy, and most of the disease is in an unresectable state when repeat recurrence is detected. In our series, 27 patients developed repeat recurrence within 6 months. Two patients underwent additional surgery, and the others received systemic chemotherapy, with a median survival time of 15 months. Considering these results, because their median survival was worse than that of patients who received systemic chemotherapy, the patients must have already had systemic disease at the time of surgery. Interestingly, we found that the patients who developed recurrence after 1999, when we started chemotherapy with irinotecan, had much better survival than those before 1998. This result seems mainly attributable to progress in chemotherapy, although diagnostic modality and perioperative management have been improved during these periods, and such improvements may have influenced survival. Now that we are in an era of effective chemotherapy, the indications for second liver resection need to be reconsidered. To improve the results of second hepatectomy, it is necessary to identify patients whose disease is likely to develop early repeat recurrence and who therefore should receive systemic chemotherapy.

Several studies have tried to identify factors predictive of a favorable outcome after repeat hepatectomy. To date, three reports have identified independent prognostic factors by multivariate analysis. Adam et al.[6] showed that the disease-free interval between initial and second liver resections and a second liver resection with curative intent were independently associated with survival. In our study, univariate analysis showed that a disease-free interval of more than 6 months between the first hepatectomy and recurrence was a significant prognostic factor, although it did not reach statistical significance by multivariate analysis. Our multivariate analysis showed that synchronous first hepatectomy was an independently predictive factor. Petrowsky et al.[18] showed that the presence of multiple lesions at repeat hepatectomy and a maximum tumor size exceeding 5 cm were independent prognostic factors after repeat hepatectomy. The third report, by Yamamoto et al.[15] from our hospital in 1999, involved data from 90 repeat hepatectomies (second = 75; third = 12; fourth = 3). Multivariate analysis revealed two independent prognostic factors after the second hepatectomy: four or more tumors, and the presence of extrahepatic disease. The present study detected three independent prognostic factors: synchronous first hepatectomy, four or more lesions evident at the second hepatectomy, and invasions of the portal vein or hepatic vein at the first hepatectomy. Thus, only the number of lesions was a common predictor of outcome, whereas the other factors differed from those highlighted in the first study. We speculate that the reason for this difference was patient selection. In

the prior report, 12 of the 75 patients who underwent second hepatectomy had received their first hepatectomy at other hospitals. In the present series, all the patients had undergone both first and second hepatectomies at our hospital. This means that we had full access to pathologic data from both procedures, ruling out any possibility that the first resection had been an incomplete one, and had not been performed at a specialized center such as ours. Okano et al.[27] reported that portal vein invasion, hepatic vein invasion, neural invasion, and absence of macroscopic bile duct invasion were prognostic factors for poor outcome in patients undergoing initial hepatectomy. Similarly, we found that histopathologic evidence of invasions of the portal vein or hepatic vein at the first hepatectomy were associated with poor prognosis in patients undergoing a second hepatectomy. To date, to our knowledge, no previous report has indicated that pathological findings other than surgical margin can be predictive of survival after second hepatectomy. It is therefore suggested that not only adequate hepatic resection but also detailed examination by a specialized pathologist is important for more precise selection of patients for second hepatectomy.

All three independent risk factors we found to be important can be recognized before the second hepatectomy, thus permitting a prognosis to be estimated before patients undergo a second hepatectomy. We grouped the patients according to their risk factors. Survival expectancies at 5 years for patients with no risk factors, with one or two, and with three risk factors were 62%, 31%, and 0%, respectively. Considering these results, second hepatectomy will most benefit patients with no risk factors. In addition, no further treatments are needed for those patients. Patients with one or two of these risk factors may require adjuvant therapy after a second hepatectomy to improve survival. There is not much evidence of the efficacy of chemotherapy after hepatectomy, even now. So far, no evidence of improved overall survival has been shown, but the tested regimens included only fluorouracil, floxuridine, and leucovorin, and did not include irinotecan or oxaliplatin.[28–30] A clinical trial comparing progression-free interval in patients undergoing surgical resection and/or ablation for hepatic metastases from colorectal cancer treated with adjuvant therapy comprising oxaliplatin and capecitabine versus without hepatic arterial infusion of floxuridine was conducted by National Surgical Adjuvant Breast and Bowel Project (NSABP-C09). This year, we are going to start a comparative trial to evaluate the efficacy of adjuvant chemotherapy with oxaliplatin added to the simplified bimonthly 5-FU and leucovorin regimen[31] as compared with surgery alone in patients undergoing curative hepatectomy. These results will permit us to determine the strategy to take with patient treatment after hepatectomy.

Generally, neoadjuvant chemotherapy for the patients with hepatic metastases is the strategy for initially unresectable tumors. Adam et al.[32] showed the results of neoadjuvant chemotherapy in 701 patients with initially unresectable colorectal liver metastases. Ninety-five cases (13.5%) were found to be resectable, and patients underwent a potentially curative resection with a 5-year survival rate of 35%. Tanaka et al.[33] studied neoadjuvant chemotherapy for 48 patients with five or more bilobar hepatic metastases. They found that 25 patients with neoadjuvant chemotherapy had a better 5-year survival rate than 23 patients who did not receive neoadjuvant chemotherapy (39 vs. 21%, $P = .039$). Multivariate analysis showed that neoadjuvant chemotherapy was an independent predictor of survival. Adam et al.[6] have adopted neoadjuvant chemotherapy for recurrent liver metastases before second hepatectomy, except in patients with small and solitary disease without concomitant extrahepatic disease.

Neoadjuvant chemotherapy before hepatectomy carries a risk of missing the opportunity for resection in patients whose tumors are initially resectable if tumor progression subsequently occurs during the course of chemotherapy. On the other hand, immediate resection carries a risk of missing occult metastases in the liver or at other sites. It was pointed out that the risk of missing the opportunity for resection could be avoided by frequent evaluation and the use of effective currently available chemotherapy regimens. Allen et al.,[34] in a study of neoadjuvant chemotherapy for patients with synchronous liver metastases, reported that none of those tumors became unresectable during the course of chemotherapy. Leonard et al.[35] commented that the role of neoadjuvant chemotherapy in patients with resectable liver metastases was not confirmed, and well-designed prospective trials were needed. One clinical trial was conducted to evaluate the feasibility and risks of the preoperative chemotherapy with oxaliplatin, 5-FU, and leucovorin and surgery for resectable colorectal liver metastases by the European Organization for Research and Treatment of Cancer.[36] The trial had been closed, and the interim results were that 93% of the patients receiving preoperative chemotherapy underwent surgery, and their surgery-related mortality and morbidity were

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A Case of Resected Huge Ileocolonic Mesenteric Liposarcoma which Responded to Pre-operative Chemotherapy using Doxorubicin, Cisplatin and Ifosfamide

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Primary mesenteric liposarcoma is a rare entity that has been reported only 14 times in English literature. The treatment strategy for mesenteric liposarcoma is, if no distant metastases are detected, surgical resection with a wide surgical margin, often followed by radiation and/or adjuvant chemotherapy for high-risk patients. However, the efficacy of pre-operative chemotherapy is unknown. If the tumor is shrunk by pre-operative chemotherapy, we could achieve complete surgical resection, which is difficult when the tumor is too large or is invading neighboring organs. We herein describe a case of huge mesenteric liposarcoma that showed significant tumor shrinkage by pre-operative chemotherapy using doxorubicin, cisplatin and ifosfamide, allowing a margin-negative operation.

Key words: mesenteric liposarcoma – preoperative chemotherapy – doxorubicin – ifosfamide

INTRODUCTION

Primary mesenteric liposarcoma is a rare entity which has been reported only 14 times in English literature (1–3), the treatment strategy for which is so far undetermined. Generally, if no distant metastases are detected, the treatment of choice is surgical resection with a wide surgical margin, often followed by radiation and/or adjuvant chemotherapy for high-risk patients. Although it is controversial whether pre-operative chemotherapy is effective, it has two oncological merits: a higher possibility of complete resection if the tumor shrinks, and the possibility of gaining pathological information about the anti-tumor effect of drugs in order to select chemotherapy drugs. Here we describe a case of huge mesenteric liposarcoma that showed significant tumor shrinkage by pre-operative chemotherapy using doxorubicin, cisplatin and ifosfamide, resulting in a margin-negative operation.

CASE REPORT

A 30-year-old man noticed abdominal distention in January 2003. He underwent a CT scan at a local hospital, which revealed a huge mass in the abdominal cavity. Fine needle biopsy was performed and the pathological diagnosis of myxoid liposarcoma was made. He was referred to our hospital in April 2003. Physical examination showed a remarkably distended abdomen. Based on the radiological data, the clinical diagnosis was made as myxoid liposarcoma in the retroperitoneum; however, the tumor was considered too huge to resect out completely because of the possibility of invasion to intestine, right kidney and abdominal wall (Fig. 1). Therefore, our treatment of choice was systemic chemotherapy. The patient underwent two courses of chemotherapy with doxorubicin (50 mg/m^2/day, on days 1–2) and cisplatin (50 mg/m^2/day, on days 1–2) every 4 weeks, followed by ifosfamide (4.9 mg/m^2/day, on days 1–5) every 5 weeks with an intention of further tumor shrinkage. After another two cycles of ifosfamide, the CT scan showed a remarkable reduction of the tumor volume, about a 50% decrease in the longest diameter of the target lesion, which was assessed as partial response. At that time, we considered that the tumor might be resectable with some combined resection (Fig. 2). After one more additional course of doxorubicin and cisplatin chemotherapy, the operation was performed in September 2003. At laparotomy, the tumor was actually located in the mesentery of the terminal ileum and right-sided colon, not in the retroperitoneum. It was a yellowish soft tumor with a diameter of 30 cm and was

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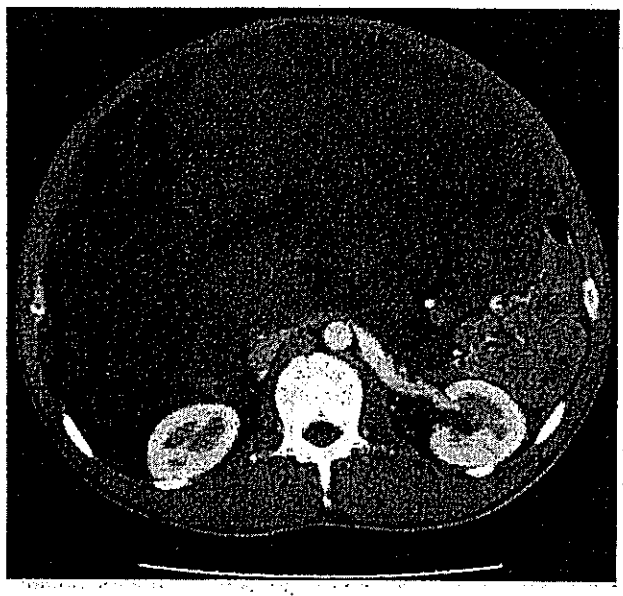

Figure 1. Pre-operative enhanced computed tomography. The peritoneal cavity was almost totally occupied by the huge tumor and an extremely distended abdomen was found.

involved in the mesentery from the ascending colon to the middle of the transverse colon. There was no peritoneal dissemination, no ascites, or no invasion to adjacent organs in the abdominal cavity. After mobilization of the right-sided colon and proximal ligation of ileocolic vessels and the right branch of the middle colic vessels, the large mesenteric tumor was resected with no macroscopic margin, in combination with the terminal ileum and right-sided colon. The post-operative course was uneventful. Histological diagnosis of the resected specimen was myxoid liposarcoma, and the proliferation of spindle cells with microcystic stromal change and adipocytic differentiation was observed. Tumor necrosis was found in less than 50%. The surgical margin was negative and there was no lymph-node involvement. However, a macroscopically sufficient surgical margin around where the feeding artery came off the superior mesenteric artery was not obtained; therefore, the patient underwent post-operative irradiation of 45 Gy along the superior mesenteric artery. The patient was well without any evidence of recurrence for 26 months after the operation; however, he has now developed abdominal recurrence and is receiving systemic chemotherapy with the same drugs, because the resected specimen showed moderate necrosis.

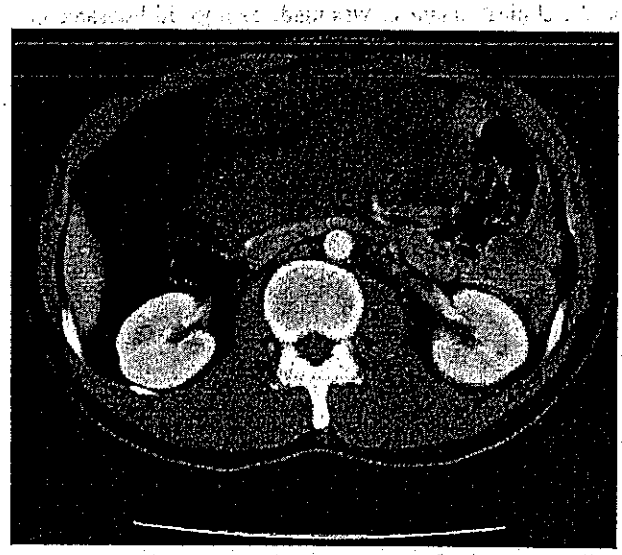

Figure 2. Enhanced computed tomography after chemotherapy. After chemotherapy, the huge tumor shrank remarkably and a normal intra-abdominal structure was seen.

DISCUSSION

Liposarcoma is the second most common soft tissue sarcoma in adults. The two major locations of liposarcama are the extremities and the retroperitoneum (4–7). Liposarcoma of the mesentery is rare, only 14 cases of which have been reported to date, based on the search in PubMed (1966–December 2005) with the keywords sarcoma, liposarcoma, or mesentery (1–3).

Liposarcoma is currently classified into three groups: well-differentiated liposarcoma with or without dedifferentiation, myxoid and round cell/cellular myxoid liposarcoma, and plemorphic liposarcoma (8). Among all liposarcomas, myxoid liposarcoma is the most common type, found in approximately 50% of cases. These histologic subtypes correlate well with the prognosis of the patient. Evans reported that the median survival of patients with the well-dedifferentiated type, the myxoid type, the dedifferentiated type and plemorphic type was 119, 113, 59 and 24 months, respectively. Myxoid liposarcoma has definite metastatic potential but a relatively indolent natural history (9).

Basically, the treatment strategy for mesenteric liposarcoma is the same as that for retroperitoneal liposarcoma (10). The treatment of choice for such liposarcoma is surgical resection with sufficient surgical margin (6,7), often followed by radiation and/or adjuvant chemotherapy with a high risk of relapse, such as for large tumors or low-grade tumors. The key chemotherapy drug is doxorubicin. Meta-analysis of 14 randomized trials of adjuvant therapy for soft tissue sarcoma in adults showed evidence that adjuvant doxorubicin-based chemotherapy significantly improves the time to local and distant recurrence and overall recurrence-free survival, and tends to improve overall survival (11). Patel et al. reported the efficacy of systemic chemotherapy using doxorubicin and dacarbazine for 21 patients with myxoid liposarcoma. The objective response rate was 44% (21–67%, 95% confidence interval), which was similar to that reported in many other studies on soft tissue sarcomas. They concluded that doxorubicin and dacarbazine-based chemotherapy was effective in treating myxoid liposarcoma (4). Ifosfamide is also an active chemotherapeutic agent in the treatment of sarcomas. Both doxorubicin and

ifosfamide have been demonstrated to show a dose–response relationship (12,13). A phase II study to evaluate the efficacy of dose-intensive doxorubicin plus ifosfamide for metastatic sarcoma or primary sarcomas with a high-risk of metastasis showed a high response rate. Patel et al. (doxorubicin 90 mg/m^2, ifosfamide 12.5 g/m^2 or doxorubicin 70 mg/m^2, ifosfamide 10 g/m^2) reported a response rate of 66% (46–82%, 95% confidence interval) (14) and De Pas et al. (doxorubicin 60 mg/m^2, ifosfamide at 10 g/m^2 with granulocyte colony-stimulating factor) showed a response rate of 50% (23–77%, 95% confidence interval) (15). This high-dose combination chemotherapy, anthracycline and ifosfamide, is thought to be the most hopeful regimen for soft tissue sarcoma and many studies using these drugs have been conducted (16,17). In the case of our patient, we adopted combination therapy of cisplatin and doxorubicin in the hope of further tumor reduction, because cisplatin is commonly used for the treatment of soft tissue sarcoma (18–20) as in our routine treatment.

There is relatively little data for the use of pre-operative chemotherapy in the treatment of soft tissue sarcomas. Casper et al. reported the outcome of a prospective trial of pre-operative and post-operative adjuvant combination chemotherapy for adults with high-grade soft tissue sarcoma (21). Twenty-nine patients with primary or recurrent soft tissue sarcoma were treated with two pre-operative cycles of cyclophosphamide 500 mg/m^2, doxorubicin 60 mg/m^2 and dacarbazine 1000 mg/m^2 before definitive surgery and radiation. Only one patient demonstrated a clinical partial response. However, intratumoral hemorrhage, cystic necrosis and liquefaction were noted regularly in the resected specimens with three tumors showing more than 90% necrosis. Most patients did not receive post-operative chemotherapy. The median time free from distant metastasis was 28 months; median survival was 35 months. These results were not superior to historical studies with no chemotherapy, or with post-operative doxorubicin. Other retrospective studies showed outcomes that responders to chemotherapy had a better overall survival than no responders; however, there was no evidence of survival improvement with pre-operative chemotherapy (22,23).

Complete surgical resection at the time of primary presentation is likely to give a chance for long-term survival (6,7,10,24–26) as well as distant recurrence-free survival (24), and positive surgical margins are the main predictors of local relapse (27,28). Because most mesenteric and retroperitoneal sarcoma are large, it is difficult to obtain adequate margins of resection and the presence of normal organs such as the gastrointestinal tract, kidney and liver make the delivery of therapeutic doses of radiation therapy either difficult or impossible. Although pre-operative chemotherapy might give no evident survival benefit, it is possible to spare adjacent normal organs and to facilitate margin-negative surgery if the primary tumor shrinks. In addition, pre-operative chemotherapy can guide post-operative treatment based on a pathologic review of the tissue after chemotherapy. This patient developed recurrence 26 months after the operation. Because the chemotherapy administered pre-operatively was effective from the histological findings of the resected specimen, which showed some extent of necrosis, we have been giving him the same combination chemotherapy. In our case, we considered before surgery that it was impossible to resect the large tumor completely. However, remarkable shrinkage of the tumor by means of pre-operative chemotherapy enabled us to perform margin-negative surgery without combined resection of adjacent organs. No patient can be considered as a candidate for long-term survival without macroscopically complete resection and this patient clearly had a chance to benefit from pre-operative chemotherapy. Although it remains unknown what kind of drugs are the most effective and how long the drugs should be administered in this pre-operative setting, we think that pre-operative chemotherapy is likely to be worth trying for patients with large liposarcoma of the abdominal and retro-abdominal cavity.

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