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.

REFERENCES

1. Ajiki W, Tsukuma H, Oshima A. Research Group for Population-based Cancer Registration in Japan. Cancer incidence and incidence rates in Japan in 1999: estimates based on data from 11 population-based cancer registries. Jpn J Clin Oncol 2004;34:352–6.

2. Ueno M, Muto T, Oya M, Ota H, Azekura K, Yamaguchi T. Multiple primary cancer: an experience at the cancer institute hospital with special reference to colorectal cancer. Int J Clin Oncol 2003;8:162–7.

3. Tomoda H, Taketomi A, Kohnoe S, Seo Y, Saito T. Second primary multiple primary cancers in Japanese hereditary nonpolyposis colorectal cancer. Oncol Rep 1998;5:143–5.

4. Maruyama H, Hasuike Y, Furukawa J, et al. Multiple colorectal carcinomas and colorectal carcinoma associated with multiple primary malignancies. Surg Today 1992;22:99–104.

5. Kobayashi Y, Arimoto H, Watanabe S. Occurrence of multiple primary cancer at the National Cancer Center Hospital, 1962–1989. Jpn J Clin Oncol 1991;21:233–51.

6. Warren S, Gates O. Multiple primary malignant tumors: a survey of the literature and a statistical study. Am J Cancer 1932;16:1358–414.

7. Research Group for Population-based Cancer Registration in Japan. Cancer incidence in Japan. In: Tajima K, Kuroishi T, Oshima A, eds. Gann monograph on cancer research: cancer mortality and morbidity statistics. Tokyo: Japan Scientific Societies Press, 2004:95–130.

8. Anonymous. Cancer incidence in Japan, 1985–89: re-estimation based on data from eight population-based cancer registries. The Research Group for Population-based Cancer Registration in Japan. Jpn J Clin Oncol 1998;28:54–67.

9. Anonymous. Cancer incidence and incidence rates in Japan in 1988: estimates based on data from ten population-based cancer registries. The Research Group for Population-based Cancer Registration in Japan. Jpn J Clin Oncol 1994;24:299–304.

10. Tomoda H, Taketomi A, Baba H, Kohnoe S, Seo Y, Saito T. Multiple primary colorectal and gastric carcinoma in Japan. Oncol Rep 1998;5:147–9.

11. Ikeda Y, Mori M, Kajiyama K, Haraguchi Y, Sugimachi K. Multiple primary gastric and colorectal cancer in Japan. Int Surg 1995;80:37–40.

12. Ioka A, Tsukuma H, Ajiki W, Oshima A. Trends in uterine cancer incidence in Japan 1975–98. Jpn J Clin Oncol 2003;33:645–6.

13. Forey B, Hamling J, Lee P, Wald N. International smoking statistics. London: Oxford, 2002.

14. Colangelo LA, Gapstur SM, Gann PH, Dyer AR. Cigarette smoking and colorectal carcinoma mortality in a cohort with long-term follow-up. Cancer 2004;100:288–93.

15. Slattery ML, Samowtiz W, Ma K, et al. CYP1A1, cigarette smoking, and colon and rectal cancer. Am J Epidemiol 2004;160:842–52.

16. Otani T, Iwasaki M, Yamamoto S, et al. Alcohol consumption, smoking, and subsequent risk of colorectal cancer in middle-aged and elderly Japanese men and females: Japan Public Health Center-based prospective study. Cancer Epidemiol Biomarkers Prev 2003;12:1492–500.

17. Dunlop MG, Farrington SM, Carothers AD, et al. Cancer risk associated with germline DNA mismatch repair gene mutations. Hum Mol Genet 1997;6:105–10.

18. Aarnio M, Mecklin JP, Aaltonen LA, Nystrom-Lahti M, Jarvinen HL. Life-time risk of different cancers in hereditary non-polyposis colorectal cancer (HNPCC) syndrome. Int J Cancer 1995;64:430–3.

19. Kawakami K, Yasutomoi M, Baba S. Analysis of the HNPCC registries data reported at the 43rd Japanese Society for Cancer of the Colon and Rectum (JSCCR) meeting. In: Baba S, ed. New strategies for treatment of hereditary colorectal cancer. Tokyo: Churchill Livingstone, 1996:229–33.

20. Utsunomiya J, Miyaki M. Studies of hereditary non-polyposis colorectal cancer in Japan. Int J Clin Oncol 1998;3:53–74.

21. Watson P, Vasen HF, Mecklin JP, Jarvinen H, Lynch HT. The risk of endometrial cancer in hereditary non-polyposis colorectal cancer. Am J Med 1994;96:516–20.

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

Seiji Ishiguro, MD,[1] Takayuki Akasu, MD,[1] Yoshiya Fujimoto, MD,[1]
Junji Yamamoto, MD,[2] Yoshihiro Sakamoto, MD,[2] Tsuyoshi Sano, MD,[2]
Kazuaki Shimada, MD,[2] Tomoo Kosuge, MD,[2] Seiichiro Yamamoto, MD,[1]
Shin Fujita, MD,[1] and Yoshihiro Moriya, MD[1]

[1]Colorectal Surgery Division, National Cancer Center Hospital, 5-1-1, Tsukiji, Chuo-ku, Tokyo, 104-0045, Japan
[2]Hepatobiliary and Pancreatic Surgery Division, National Cancer Center Hospital, 5-1-1, Tsukiji, Chuo-ku, Tokyo, 104-0045, Japan

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,

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

Ann. Surg. Oncol. Vol. 13, No. 12, 2006

364

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
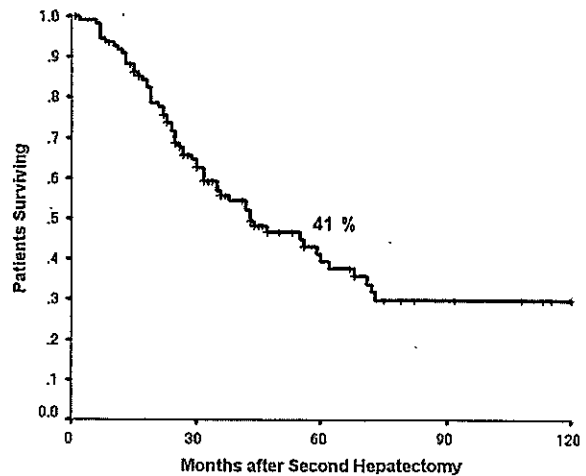

FIG. 1. Overall survival after second hepatectomy in patients with colorectal liver metastases.

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-dihydroxy-pyridine/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
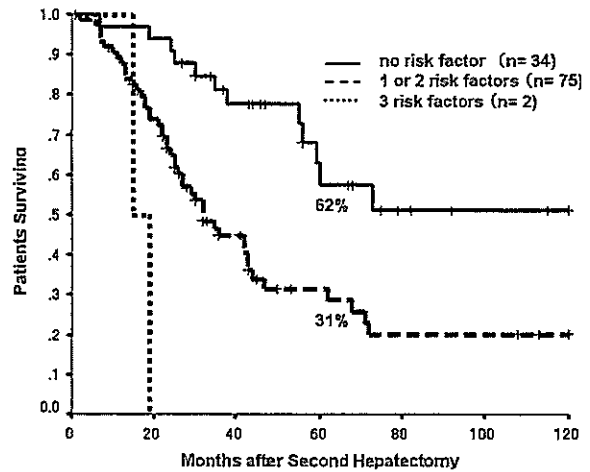

FIG. 2. Overall survival according to groups divided by number of risk factors identified in current study.

within 6 months and died at 15 months and 19 months, respectively, after the second hepatectomy.

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

24. Simmonds PC. Palliative chemotherapy for advanced colo-rectal cancer: systematic review and meta-analysis. Colorectal Cancer Collaborative Group. *BMJ* 2000; 321:531–5.

25. Tournigand C, Andre T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol* 2004; 22:229–37.

26. Goldberg RM, Sargent DJ, Morton RF, et al. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol* 2004; 22:23–30.

27. Okano K, Yamamoto J, Moriya Y, et al. Macroscopic intrabiliary growth of liver metastases from colorectal cancer. *Surgery* 1999; 126:829–34.

28. Kemeny N, Huang Y, Cohen AM, et al. Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer. *N Engl J Med* 1999; 341:2039–48.

29. Kemeny M. Hepatic artery infusion of chemotherapy as a treatment for hepatic metastases from colorectal cancer. *Cancer J* 2002; 8(suppl 1):S82–8.

30. Kemeny N, Eid A, Stockman J, et al. Hepatic arterial infusion of floxuridine and dexamethasone plus high-dose Mitomycin C for patients with unresectable hepatic metastases from colorectal carcinoma. *J Surg Oncol* 2005; 91:97–101.

31. Maindrault-Goebel F, Louvet C, Andre T, et al. Oxaliplatin added to the simplified bimonthly leucovorin and 5-fluoro-uracil regimen as second-line therapy for metastatic colorectal cancer (FOLFOX6). GERCOR. *Eur J Cancer* 1999; 35:1338–42.

32. Adam R, Avisar E, Ariche A, et al. Five-year survival following hepatic resection after neoadjuvant therapy for nonresectable colorectal [liver] metastasis. *Ann Surg Oncol* 2001; 8:347–53.

33. Tanaka K, Adam R, Shimada H, Azoulay D, Levi F, Bismuth H. Role of neoadjuvant chemotherapy in the treatment of multiple colorectal metastases to the liver. *Br J Surg* 2003; 90:963–9.

34. Allen PJ, Kemeny N, Jarnagin W, DeMatteo R, Blumgart L, Fong Y. Importance of response to neoadjuvant chemotherapy in patients undergoing resection of synchronous colorectal liver metastases. *J Gastrointest Surg* 2003; 7:109–15; discussion 16–7.

35. Leonard GD, Brenner B, Kemeny NE. Neoadjuvant chemotherapy before liver resection for patients with unresectable liver metastases from colorectal carcinoma. *J Clin Oncol* 2005; 23:2038–48.

36. Nordlinger B, Sorbye H, Debois M, et al. Feasibility and risks of pre-operative chemotherapy (CT) with FOLFOX 4 and surgery for resectable colorectal cancer liver metastases (LM). Interim results of the EORTC Intergroup randomized phase III study 40983 (abstract). *J Clin Oncol* 2005; 23(16 suppl):3528.

Ann. Surg. Oncol. Vol. 13, No. 12, 2006

370

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

Seiji Ishiguro, Seiichiro Yamamoto, Hirokazu Chuman and Yoshihiro Moriya

Colorectal Surgery Division, National Cancer Center Hospital, Tokyo, Japan

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

For reprints and all correspondence: Seiichiro Yamamoto, Colorectal Surgery Division, National Cancer Center Hospital, 5-1-1 Tsukiji Tyuo-ku, Tokyo 104-0045, Japan. E-mail: sishigur@ncc.go.jp

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/m²/day, on days 1–2) and cisplatin (50 mg/m²/day, on days 1–2) every 4 weeks, followed by ifosfamide (4.9 mg/m²/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
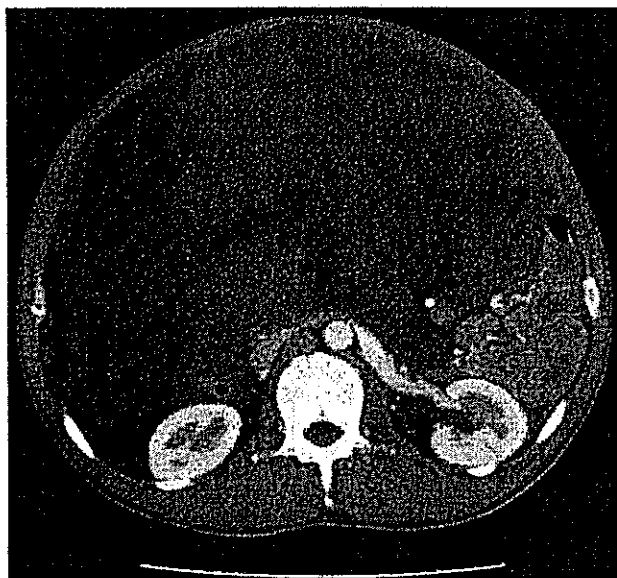
Figure 1. Pre-operative enhanced computed tomography. The peritoneal cavity was almost totally occupied by the huge tumor and an extremely distended abdomen was found.

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 microcyctic stromal
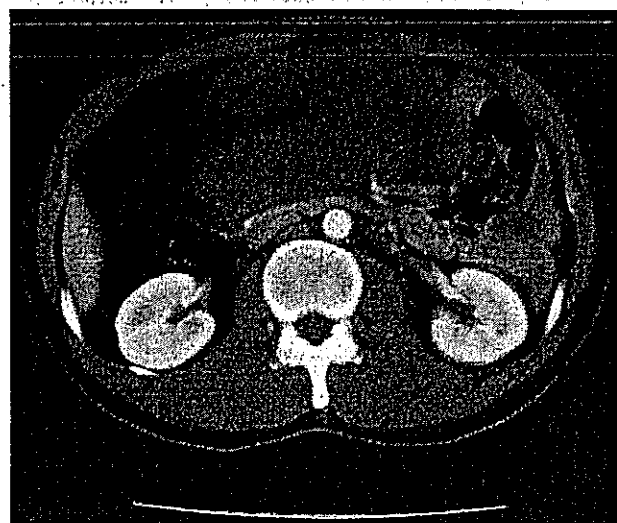

Figure 2. Enhanced computed tomography after chemotherapy. After chemotherapy, the huge tumor shrank remarkably and a normal intra-abdominal structure was seen.

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.

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/m², ifosfamide 12.5 g/m² or doxorubicin 70 mg/m², ifosfamide 10 g/m²) reported a response rate of 66% (46—82%, 95% confidence interval) (14) and De Pas et al. (doxorubicin 60 mg/m², ifosfamide at 10 g/m² 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/m², doxorubicin 60 mg/m² and dacarbazine 1000 mg/m² 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.

References

1. Goel AK, Sinha S, Kumar A, Karak AK, Chattopadhyay TK. Liposarcoma of the mesocolon — case report of a rare lesion. *Surg Today* 1994;24:1003—6.
2. Amato G, Martella A, Ferraraccio F, Di Martino N, Maffettone V, Landolfi V, et al. Well differentiated 'lipoma-like' liposarcoma of the sigmoid mesocolon and multiple lipomatosis of the rectosigmoid colon. Report of a case. *Hepatogastroenterology* 1998;45:2151—6.
3. Nakamura A, Tanaka S, Takayama H, Sakamoto M, Ishii H, Kusano M, et al. A mesenteric liposarcoma with production of granulocyte colony-stimulating factor. *Intern Med* 1998;37:884—90.
4. Patel SR, Burgess MA, Plager C, Papadopoulos NE, Linke KA, Benjamin RS. Myxoid liposarcoma. Experience with chemotherapy. *Cancer* 1994;74:1265—9.
5. Laurino L, Furlanetto A, Orvieto E, Del Tos AP. Well-differentiated liposarcoma (atypical lipomatous tumors). *Semin Diagn Pathol* 2001;18:258—62.
6. Lewis JJ, Leung D, Woodruff JM, Brennan MF. Retroperitoneal soft-tissue sarcoma: analysis of 500 patients treated and followed at a single institution. *Ann Surg* 1998;228:355—65.
7. Mendenhall WM, Zlotecki RA, Hochwald SN, Hemming AW, Grobmyer SR, Cance WG. Retroperitoneal soft tissue sarcoma. *Cancer* 2005;104:669—75.
8. Hasegawa T, Seki K, Hasegawa F, Matsuno Y, Shimodo T, Hirose T, et al. Dedifferentiated liposarcoma of retroperitoneum and mesentery: varied growth patterns and histological grades — a clinicopathologic study of 32 cases. *Hum Pathol* 2000;31:717—27.
9. Evans HL. Liposarcoma: a study of 55 cases with a reassessment of its classification. *Am J Surg Pathol* 1979;3:507—23.
10. Heslin MJ, Lewis JJ, Nadler E, Newman E, Woodruff JM, Casper ES, et al. Prognostic factors associated with long-term survival for retroperitoneal sarcoma: implications for management. *J Clin Oncol* 1997;15:2832—9.
11. Adjuvant chemotherapy for localised resectable soft-tissue sarcoma adults: meta-analysis of individual data. Sarcoma Meta-analysis Collaboration. *Lancet* 1997;350:1647—54.
12. O'Bryan RM, Baker LH, Gottlieb JE, Rivkin SE, Balcerzak SP, Grumet GN, et al. Dose response evaluation of adriamycin in human neoplasia. *Cancer* 1977;39:1940—8.
13. Benjamin RS, Legha SS, Patel SR, Nicaise C. Single-agent ifosfamide studies in sarcomas of soft tissue bone: the M.D. Anderson experience. *Cancer Chemother Pharmacol* 1993;39(Suppl 2):S174—9.
14. Patel SR, Vadhan-Raj S, Burgess MA, Plager C, Papadopolous N, Jenkins J, et al. Results of two consecutive trials of dose-intensive

chemotherapy with doxorubicin and ifosfamide in patients with sarcomas. *Am J Clin Oncol* 1998;21:317–21.

15. De Pas T, De Braud F, Orlando L, Nole F, Munzone E, Zampino MG, et al. High-dose ifosfamide plus adriamycin in the treatment of adult advanced soft tissue sarcomas: is it feasible? *Ann Oncol* 1998;9:917–9.

16. Frustaci S, Gherlinzoni F, De Paoli A, Bonetti M, Azzarelli A, Comandone A, et al. Adjuvant chemotherapy for adult soft tissue sarcomas of the extremities and girdles: results of the Italian randomized cooperative trial. *J Clin Oncol* 2001;19:1238–47.

17. Gortzak E, Azzarelli A, Buesa J, Bramwell VH, van Coevorden F, van Geel AN, et al. A randomised phase II study on neo-adjuvant chemotherapy for 'high-risk' adult soft-tissue sarcoma. *Eur J Cancer* 2001;37:1096–103.

18. Edmonson JH, Long HJ, Richardson RL, Creagan ET, Green SJ. Phase II study of a combination of mitomycin, doxorubicin and cisplatin in advanced sarcomas. *Cancer Chemother Pharmacol* 1985;15:181–2.

19. Stephens FO, Tattersall MH, Marsden W, Waugh RC, Green D, McCarthy SW. Regional chemotherapy with the use of cisplatin and doxorubicin as primary treatment for advanced sarcomas in shoulder, pelvis, and thigh. *Cancer* 1987;60:724–35.

20. Bacci G, Picci P, Ferrari S, Ruggieri P, Casadei R, Tienghi A, et al. Primary chemotherapy and delayed surgery for nonmetastatic osteosarcoma of the extremities. Results in 164 patients pre-operatively treated with high doses of methotrexate followed by cisplatin and doxorubicin. *Cancer* 1993;72:3227–38.

21. Casper ES, Gaynor JJ, Harrison LB, Panicek DM, Hajdu SI, Brennan MF. Operative and postoperative adjuvant combination chemotherapy for adults with high grade soft tissue sarcoma. *Cancer* 1994;73:1644–51.

22. Rouesse JG, Friedman S, Sevin DM, le Chevalier T, Spielmann ML, Contesso G, et al. Preoperative induction chemotherapy in the treatment of locally advanced soft tissue sarcomas. *Cancer* 1987;60:296–300.

23. Pezzi CM, Pollock RE, Evans HL, Lorigan JG, Pezzi TA, Benjamin RS, et al. Preoperative chemotherapy for soft-tissue sarcomas of the extremities. *Ann Surg* 1990;211:476–81.

24. Malerba M, Doglietto GB, Pacelli F, Carriero C, Caprino P, Piccioni E, et al. Primary retroperitoneal soft tissue sarcomas: results of aggressive surgical treatment. *World J Surg* 1999;23:670–5.

25. Eilber FC, Eilber KS, Eilber FR. Retroperitoneal sarcomas. *Curr Treat Options Oncol* 2000;1:274–8.

26. Stojadinovic A, Leung DH, Hoos A, Jaques DP, Lewis JJ, Brennan MF. Analysis of the prognostic significance of microscopic margins in 2,084 localized primary adult soft tissue sarcomas. *Ann Surg* 2002;235:424–34.

27. Pisters PW, Leung DH, Woodruff J, Shi W, Brennan MF. Analysis of prognostic factors in 1,041 patients with localized soft tissue sarcomas of the extremities. *J Clin Oncol* 1996;14:1679–89.

28. Stefanovski PD, Bidoli E, De Paoli A, Buonadonna A, Boz G, Libra M, et al. Prognostic factors in soft tissue sarcomas: a study of 395 patients. *Eur J Surg Oncol* 2002;28:153–64.

直腸癌局所再発に対する拡大手術
仙骨合併骨盤内臓全摘術
Total pelvic exenteration with distal sacretomy for fixed recurrent rectal cancer

上原　圭介*　　山本聖一郎*　　藤　田　　伸*
Keisuke Uehara　　Seiichiro Yamamoto　　Shin Fujita

赤須　孝之*　　森谷　冝皓**
Takayuki Akasu　　Yoshihiro Moriya

●要旨●仙骨合併骨盤内臓全摘術（TPES）は骨盤壁に浸潤の及ぶ局所再発直腸癌に対して，仙骨を含む隣接臓器とともに腫瘍を *en bloc* に摘出し，free surgical margin が確保できる根治的治療である。71例の再発直腸癌に対してTPES を行ってきた。本稿では TPES の手術適応，手術手技，合併症の実際を概説した。R0切除率は84.5%で，R0切除症例の5年生存率は48.1%，10年生存率は40.6%と比較的良好な成績を得ている。手術侵襲は過大なゆえ，その手術適応は厳格でなくてはならず，骨盤外科に精通した外科チームのみが行うべき術式である。

● key words：仙骨合併骨盤内臓全摘術，直腸癌，局所再発

はじめに

局所再発直腸癌患者の QOL は低く，長期にわたり出血，疼痛，腸閉塞，会陰潰瘍などの難治性合併症を患い，悲惨な経過をたどる症例も少なくない。欧米では主に放射線化学療法を中心に集学的な治療が広く行われているが，いまだ満足のいく治療法は確立されていない。一方，当院では局所再発直腸癌に対して積極的に外科的切除を行ってきた。

仙骨合併骨盤内臓全摘術（total pelvic exenteration with distal sacretomy；TPES）は骨盤壁に浸潤の及ぶ局所再発直腸癌（fixed recurrent tumor；FRT）に対して，仙骨を含む隣接臓器とともに腫瘍を *en bloc* に摘出し，free surgical margin を確保する根治的治療である。本術式は1981年の Wanebo らの報告に始まり，当院では1983年から積極的に導入し，これまでに71例に対して施行してきた。現在では安定した手術手技となり，FRT に対する基本術式と位置づけている。

本稿では TPES の手術手技の実際，手術適応，合

*　　国立がんセンター中央病院大腸外科
**　同手術部部長

表1　手術適応条件

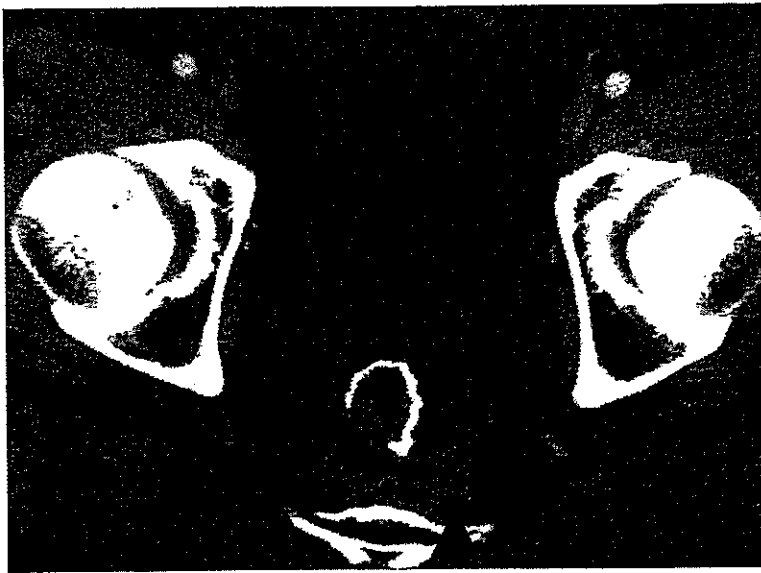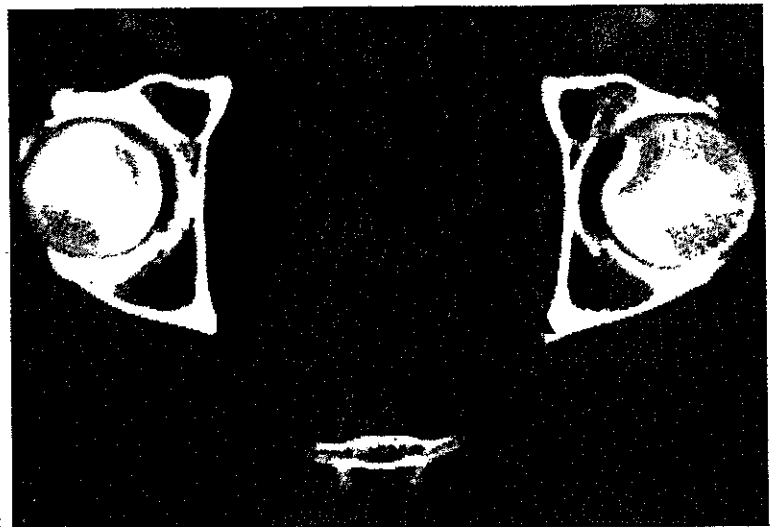| 絶対的禁忌条件 |
| --- |
| 　切除可能な肝転移以外に遠隔転移を認める |
| 相対的禁忌条件 |
| 　仙骨岬角までの進展（S2 温存不可） |
| 　外腸骨血管周囲への浸潤 |
| 　下肢に放散する疼痛 |
| 　腸骨静脈・リンパ管閉塞による下肢の浮腫 |
| 　側方リンパ節転移 |
| 　75 歳以上の高齢者 |
| 　初回手術で側方郭清が行われている |
| 　高度な動脈硬化 |
| 　低分化腺癌または印環細胞癌 |

併症および遠隔成績について述べる。

手術適応

TPES は過大な侵襲を伴う術式のため，手術適応は厳格でなくてはならない。当院における手術適応を表1に示す。原則的に切除可能な1〜2個の肝転移を除き，遠隔転移がなく，骨盤内に限局した局所再発癌のみを適応としている。下肢の浮腫，坐骨神経痛などをきたす症例は癌の神経，リンパ組織への広範な浸潤が予測され，また初回手術時に側方郭清施行症例や側方

a：吻合部および吻合部近傍再発

b：後方骨盤壁再発

c：側方骨盤壁再発

図1　TPES の適応となる再発形式

リンパ節転移を認める症例も原則的に適応外としている。

　局所再発は再発の原因とその進展状況から図1のごとく分類できる。吻合および吻合部近傍再発は吻合部断端への implantation や直腸間膜の切除不足が主な原因である。しかし進展が進めば骨盤壁再発との区別は困難となる。後方・側方骨盤壁再発は側方リンパ節転移などのリンパ系進展や剝離面での腫瘍遺残が主な

原因である。

TPES において R0手術を行うためにもっとも重要なのが上方および側方断端である。腹側には泌尿器系臓器，背側には仙骨が存在するのに対し，側方では骨盤壁に直接浸潤する。このためとくに側方骨盤壁再発症例では側方剝離断端を free にすることが手術の山場となる。術前の画像，とくに MRI による進展所見の詳細な検討と術中の内閉鎖筋や棘突起などの積極的合併切除が肝要となる。

仙骨切断レベルは術前 MRI 所見を参考に決定する。切断レベルは原則として術後歩行障害や脊髄液瘻をきたすことのない S2下縁までとしている。これより高位での仙骨切断が必要となる症例は仙骨前面の表層切除あるいは Waldeyer 筋膜のみの切除に留めている。仙骨高位での切断は原発性仙骨腫瘍に対して行われることもあるが，根治性と重篤な術後障害を天秤にかければ，再発癌に対して行うべき術式ではない。仙骨 S2以下の切断を含む本術式において合併切除可能な非骨性骨盤壁は仙棘靱帯，仙結節靱帯，尾骨筋，内閉鎖筋の一部，梨状筋および S3以下の仙骨神経となる。

手術手技

手術手順を表2に示す。

表2 手術手順

1. 腹腔操作
   ①前方（Retzius 腔）の展開と DVC（dorsal vein complex）の処理
   ②仙骨前面の展開
   ③側方郭清および内腸骨血管の処理と仙骨切断レベルの決定
2. 会陰操作
   ①肛門挙筋の切離
   ②尿道の切離
3. 体位変換，仙骨部操作
   ①大殿筋の仙骨からの切離
   ②椎弓切除，仙骨神経の確認
   ③仙骨切断
4. 体位変換，再建操作
   ①回腸導管，人工肛門の作成
   ②ドレーン挿入と閉腹

1. 腹腔操作

体位は砕石位とし，剣状突起5cm下から恥骨結合までの正中切開で開腹する。肝転移，腹膜播種，大動脈周囲リンパ節転移などの遠隔転移がなく，再発巣が骨盤内に限局していることを確認し，手術遂行の是非を決定する。

まず膀胱前腔（Retzius 腔）の展開を行う。膀胱前面を恥骨に沿って疎な組織の剝離を進めると，前立腺の前側方で恥骨前立腺靱帯と内骨盤筋膜（endopelvic fascia）が現れる。前立腺の両側で endopelvic fascia

図2 bunching method
鳶巣式 bunching 鉗子で DVC を集束し，2-0 Ti-cron で二重結紮，切離する

を電気メスで切開し肛門挙筋を露出する。続いて，前立腺表面を走行する深陰茎背静脈の深枝である dorsal vein complex（DVC）の処理を行う。鳶巣式 bunching 鉗子を用い，左右の endopelvic fascia 断端から前立腺前面に沿って組織を集束させると，この中に DVC が含まれることになる（bunching method）（図2）。鉗子の前後で二重結紮，切離する。尿道の切離は会陰操作時に行うとよい。

大動脈分岐部より仙骨骨膜を露出する層で仙骨切断予定部位まで剝離をすすめる。この操作では瘢痕組織に埋もれる仙骨前面静脈叢の確認が困難なために多少の出血を伴うが，出血部位をしっかりと確認し，吸引しながら電気凝固を行えば止血可能である。それでも止血できない場合は，綿球で圧迫し，術野の展開を十分に行った後，再度止血を試みる。

次に内腸骨血管系の処理を行う。左右総腸骨動脈から内外腸骨動脈分岐部を露出し，外腸骨血管に沿い内閉鎖筋を露出しながら内下方に剝離操作を進める。閉鎖動静脈は切離し，閉鎖神経は温存する。この操作の過程で腰仙骨神経および第1，第2仙骨神経の同定ができる。可能であれば温存すべき第2仙骨神経にテービングを行うと，仙骨切断時の神経誤認を回避できる。内腸骨動脈は上殿動脈が分岐した後で，二重結紮切離する。上殿動脈の温存は必須ではないが，会陰創の血流が悪くなるため，できるだけ温存する。内腸骨静脈本幹の切離に先立ち，骨盤壁を貫通する下殿動静脈，陰部動静脈などの末梢分枝を丁寧に結紮切離し，最後に内腸骨静脈本幹を結紮切離する。内腸骨静脈の切離を先行すれば，骨盤内静脈系のうっ血を招き，後の操作で思わぬ大出血につながる可能性がある。骨盤内静脈系からの出血コントロールがきわめて大切な本術式において，重要なポイントの1つである。

尿管は瘢痕組織のなかに埋もれているため，周囲の結合織，栄養血管をできるだけ温存しながら慎重に剝離し，左右総腸骨血管との交叉部より可及的膀胱側で切離する。一側または両側にシングルJカテーテルを挿入し，術中の尿量モニタリングを行う。

2. 会陰操作

会陰の皮膚切開は男性では直腸切断術に準じ，女性では外性器を含めた切離線で腹部創につなげる。会陰部に再発巣の浸潤が及ぶ場合には広範な会陰皮膚の切除が必要となる場合もある。
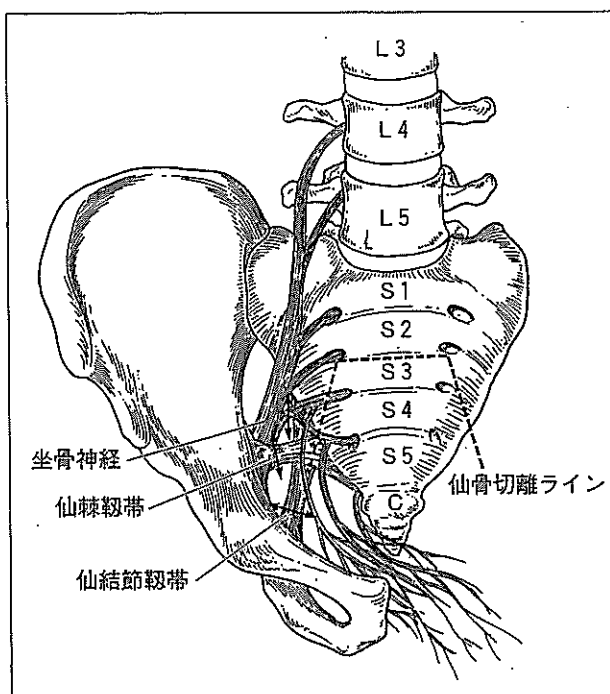
この操作での出血は骨盤底筋群のうっ血した静脈が

図3　仙骨の切離ライン

主な原因であり，出血を減らすためには内腸骨静脈本幹の結紮前に会陰操作を行っておくとよい。

3. 仙骨操作

仙骨切断操作は整形外科医の協力が必要である。腹部および会陰創の仮閉鎖を行った後，体位を砕石位から腹臥位へ変更する。注意すべき点は腹圧の上昇を避けることで，腹圧が上昇すると静脈還流が悪くなり，椎骨静脈叢の圧が上昇して仙骨切断時の出血量が増加する。われわれは椎弓切除用の4点支持架台を使用し腹圧上昇を防止している。

皮膚切開は会陰創の背側端から仙骨切断予定部位より約10cm頭側までの正中切開とする。大殿筋は後の骨盤底形成時に使用するため，仙骨骨膜に沿って剝がし，仙骨背側面を十分に露出する。ついで仙骨を固定する靱帯および筋肉の切離を行う。坐骨結節を確認後，仙結節靱帯を切離する。次いで会陰より示指を挿入し，仙棘靱帯の走行を確認後，これを坐骨棘近傍で切離する（図3）。これらの靱帯を切離した後，梨状筋の切離を行うが，梨状筋腹側には坐骨神経および仙骨神経が走行しており，損傷しないよう注意が必要である。この際，腹腔操作で行った第2仙骨神経のテービングが非常に有用となる。切離が進んだら示指で仙骨前面の剝離層を確認し，仙骨切断レベルの最終確認を行う。

仙骨切断は，まず正中仙骨稜を削り，仙骨管を開放