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Original Paper

A New Classification System for Liver Metastases from Colorectal Cancer in Japanese Multicenter Analysis

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ABSTRACT

Background/Aims: Although numerous authors have reported various prognostic factors for liver metastases from colorectal cancer, there is not yet a general classification.

Methodology: A total of 478 colorectal cancer patients from 18 institutes were studied. Prognostic factors were investigated using univariate and multivariate analyses.

Results: Independent prognostic factors for colorectal liver metastases were number of liver metastases, size of the largest liver metastases, mesenteric lymph node metastases (pN0/1: ≤3 lesions, pN2: ≥4 lesions), and extrahepatic metastases (EM0: absence of extrahepatic metastasis, EM1: presence of extrahepatic metastases). We defined the following classification system; Stage A: HT1 (≤4 lesions and ≤5cm) and pN0/1, Stage B: HT2 (≥5 lesions or >5cm) and pN0/1, or HT1 and pN2, Stage C: HT2 and pN2, HT3 (≥5 lesions and >5cm) with any pN, or any HT and any pN with EM1. Five-year survival rates were 53.5% for Stage A patients, 25.4% for Stage B patients, and 5.8% for Stage C patients. Median survival time was 70.4 months, 31.4 months, and 17.2 months, respectively.

Conclusions: Our classification was advocated to evaluate prognoses for liver metastases from colorectal cancer. It can help guide decision making in terms of liver resection and assessing patient prognosis.

KEY WORDS:
Colorectal cancer; Liver metastasis; Classification system; Prognostic factor

INTRODUCTION

The incidence of colorectal cancer is ranked second among malignant diseases in Western countries and is the second leading cause of death (1). In Japan, more than 89,000 patients develop colorectal cancer and more than 36,000 die of this disease every year (2). The liver is the most common site of distant metastasis in colorectal cancer (3). It is well known that surgical resection is the most effective treatment for liver metastases from colorectal cancer (4-7). According to recent reports, 5-year survival after hepatectomy for colorectal cancer with liver metastases is 26% to 51% (4,8-16). However, some patients develop early recurrences and do not benefit from resection. It is important to stratify patients to determine which patients will most likely benefit from resection. Currently, we do not have any general rules for the treatment of colorectal cancer with liver metastases, and published papers are based on their own rule. The purpose of this study is to advocate a new classification system that could be used to help make treatment decisions for patients with liver metastases from colorectal cancer.

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METHODOLOGY

Patients

Patients with colorectal cancer with liver metastases registered in the "Study for Establishing Treatments for Hepatic and Pulmonary Metastases from Colorectal Cancer" were studied. The patients started treatment for liver metastases from colorectal cancer at 18 institutions from January 1992 to December 1996. This patient registry was established to investigate prognostic factors in colorectal cancer patients with liver metastases from a clinicopathologic viewpoint and to determine a classification system for patients. A total of 604 patients were enrolled for the study, and 478 patients were eligible for investigation. One hundred and twenty-six patients were not eligible because of incomplete data. The number of liver metastases, size of maximum liver metastases, lymph nodes metastases of the primary tumor, and extrahepatic distant metastases were evaluated for prognostic factors. For the resectable cases, the measurement of the size and the number of liver metastases was based on pathological findings. On the other hand, for the unresectable cases, computed

tomography was used to determine the size and number as well as extrahepatic disease.

The endpoint of this study was survival time. Death from any cause was considered an event. Patients who were still alive at last follow-up with or without disease were censored. Survival time was measured from the date of first resection of liver metastases to death or to the date of the last known follow-up evaluation in resectable cases, and was measured from the date of first diagnosis of liver metastases to death or to the date of the last known follow-up evaluation in unresectable cases.

TABLE 1 Characteristics of 478 Patients with Liver Metastases from Colorectal Cancer

Characteristics	Categories and Number / Average Value (Range)	
Patients		
Gender	Male	310
	Female	168
Age		60.5 (27-94)
Primary tumor Location	Colon	273
	Rectum	205
Tumor depth	T1	7
	T2	24
	T3	410
	T4	35
	Unknown	2
Lymph node	pN0	147
	pN1	219
	pN2	112
Liver	Synchronous	277
	Metachronous	201
Maximum diameter		4.0 (0.5-23.0)
Number of metastases		2.8 (1-22)
Extrahepatic metastases	Absence	392
	Presence	86

TABLE 2 Univariate Analysis of Prognostic Factors for Liver Metastases from Colorectal Cancer

Factors	5-year survival (%)	Median survival time (mo)	*P* Value
Over all	30.7	31.4	
Maximum diameter			
≤5cm	34.4	34.1	<0.0001
≥5cm	16.8	26.4	
Number of liver metastases			
≤4 lesions	36.6	37.1	<0.0001
≥5 lesions	11.5	16.4	
Lymph node metastases			
≤3 lesions	36.8	36.2	<0.0001
≥4 lesions	13.1	21.5	
Extrahepatic metastases			
absence	36.2	35.4	<0.0001
presence	6.0	19.5	

TABLE 3 Univariate Analysis of Number of Liver Metastases

Number of Liver Metastases	Relative Risk	95% Confidence Interval Lower	Upper	*P* Value
1: ≥2	1.715	1.362	2.160	<0.0001
2≥: 3≥	2.066	1.653	2.577	<0.0001
3≥: 4≥	2.262	1.802	2.849	<0.0001
4≥: 5≥	2.326	1.818	2.967	<0.0001
5≥: 6≥	1.805	1.294	2.519	0.0005

Statistical Analysis

For patients with synchronous liver metastases, the survival period was calculated from the time of initial resection of the primary colorectal tumor. For patients with metachronous liver metastases, the survival period was calculated from the time of hepatectomy in resectable cases and was calculated from time of detection of liver metastases from colorectal cancer in unresectable cases. Survival curves were calculated using the Kaplan-Meier method. Statistical comparisons of potentially predictive factors were first performed using log-rank analysis for univariate analysis. The Cox proportional hazards model was used to perform multivariate analysis of factors related to survival. Significance was defined as $P<0.05$. All statistical evaluations were performed using Stat View® (Abacus Concepts, Inc., Berkley, California).

RESULTS

Characteristics

The clinicopathologic characteristics of eligible patients are summarized in **Table 1**. The lymph node metastases of primary tumor were pN0 in 147 patients, pN1 in 219 patients, and pN2 in 112 patients. The maximum diameter of metastatic tumors and number of liver metastases were 4.0cm (range, 0.5-23.0cm) and 2.8 (range, 1-22), respectively. Eighty-six patients had extrahepatic metastases, including hepatic hilar and para-aortic lymph node metastases; the remaining 392 patients did not have extrahepatic metastases. Of the 478 colorectal cancer patients with liver metastases, 380 cases were treated surgically. In this study, no patients were underwent radiofrequency ablation therapy.

Survival Analysis of Prognostic Factors

The 5-year survival rate was 30.7% and median survival time (MST) was 31.4 months **(Table 2)**. In our series, we examined the best point to draw the line: solitary *versus* multiple lesions, ≤2 lesions *versus* ≥3 lesions, ≤3 lesions *versus* ≥4 lesions, ≤4 lesions *versus* ≥5 lesions, ≤5 lesions *versus* ≥6 lesions **(Table 3)**. However, all of the comparisons resulted in significant statistical differences. Furthermore, ≤4 lesions *versus* ≥5 lesions had the highest relative risk (relative risk = 2.326). Therefore, the best point to draw the line was between ≤4 lesions and ≥5 lesions. Patients with ≤4 liver metastases lived significantly longer than patients with ≥5 lesions ($P<0.0001$). Survival at 5 years was 36.6% for ≤4 liver metastases patients and 11.5% for ≥5 liver metastases patients; MST was 37.1 months and 16.4 months, respectively.

We also examined the best point to draw the line in maximum size of liver metastases. When we categorized between ≤5cm and >5cm, we were able to obtain the highest relative risk and the lowest *P*

value **(Table 4)**. Patients with lesions ≤5cm lived significantly longer than patients with lesions >5cm (P<0.0001). Survival at 5 years was 34.4% in ≤5cm patients and 16.8% in >5cm patients; MST was 34.1 months and 26.4 months, respectively.

We categorized lymph nodes metastases of the primary tumor according to the tumor, node, and metastasis (TNM) classification. Patients in the pN0 and pN1 groups lived significantly longer than patients in the pN2 group (P<0.0001). Survival at 5 years was 36.8% in the pN0 and pN1 group and 13.1% in the pN2 group; MST was 36.2 months and 21.5 months, respectively. However, there were no significant differences between patients in the pN0 and pN1 groups. The 5-year survival was 33.0% in pN0 patients, 36.7% in pN1 patients, and 14.2% in pN2 patients; MST was 43.2 months, 31.3 months, and 21.9 months, respectively.

Patients with no extrahepatic metastases (EM0) lived significantly longer than patients with extrahepatic metastases (EM1) (P<0.0001). Survival at 5 years and MST, respectively, were 36.2% and 35.4 months for EM0 patients and 6.0% and 19.5 months for EM1 patients.

Multivariate Analysis and Classification for Liver Metastases from Colorectal Cancer

In the multivariate analysis, all of the prognostic factors were significantly different **(Table 5)**. Five-year survival rate was 40.1% in ≤4 lesions and ≤5cm liver metastases, 21.1% in ≤4 lesions and >5cm liver metastases, 14.2% in ≤5 lesions and ≤5cm liver metastases, and 5.2% in ≥5 lesions and >5cm liver metastases. Consequently, we defined ≤4 lesions and ≤5cm liver metastases as HT1; ≥5 lesions or >5cm liver metastases as HT2; and ≥5 lesions and >5cm liver metastases as HT3. As a result, patients with HT1 disease lived significantly longer than patients with HT2 disease (P<0.0001), who lived significantly longer than patients with HT3 disease (P<0.0001). Five-year survival rate was 39.2% in HT1 patients, 17.0% in HT2 patients, and 4.8% in HT3 patients. MST was 38.1 months, 26.0 months, and 12.0 months, respectively **(Figure 1)**.

Five-year survival rate was 48.1% in HT1 and pN0,1 patients, 22.5% in HT2 and pN0,1 patients, 7.7% in HT3 and pN0,1 patients, 18.9% in HT1 and pN2 patients, 3.1% in HT2 and pN2 patients, and 0.0% in HT3 and pN2 patients. Thus, we defined HT1 and pN0,1 as Stage A'; HT2 and pN0,1 or HT1 and pN2 as Stage B'; and HT2 and pN2 or HT3 with any pN as Stage C'. Stage A' patients lived significantly longer than Stage B' patients (P<0.0001), who lived significantly longer than Stage C' patients (P<0.0001). Five-year survival rate was 48.9% in Stage A' patients, 20.2% in Stage B' patients, and 4.0% in Stage C' patients. MST was 57.2 months, 27.4 months, and 14.7 months, respectively. Because patients with extrahepatic metastases showed poor prognosis, we defined that all of them were included in Stage C'. From the above classification, we were able to classify colorectal cancer patients with liver metastases; Stage A: HT1 and pN0/1, Stage B: HT2 and pN0/1, or HT1 and pN2, Stage C: HT2 and pN2, HT3 with any pN, or any HT and any pN with EM1

TABLE 4 Univariate Analysis of Size of Liver Metastases

Maximum Diameter of Liver Metastases	Relative Risk	95% Confidence Interval Lower	Upper	P Value
≤3cm: >3cm	1.324	1.056	1.661	0.0149
≤4cm: >4cm	1.524	1.212	1.916	0.0003
≤5cm: >5cm	1.623	1.279	2.137	<0.0001
≤6cm: >6cm	1.508	1.112	2.045	0.0081

TABLE 5 Multivariate Analysis of Prognostic Factors for Liver Metastases from Colorectal Cancer

Factors	Relative Risk	95% Confidence Interval Lower	Upper	P Value
Maximum diameter				
≤5cm : >5cm	1.692	1.305	2.193	<0.0001
Number of liver metastases				
≤4 : ≥5 lesions	2.326	1.818	2.967	<0.0001
Lymph node metastases				
≤3 : >4 lesions	1.880	1.468	2.404	<0.0001
Extrahepatic metastases				
absence : presence	2.232	1.706	2.915	<0.0001

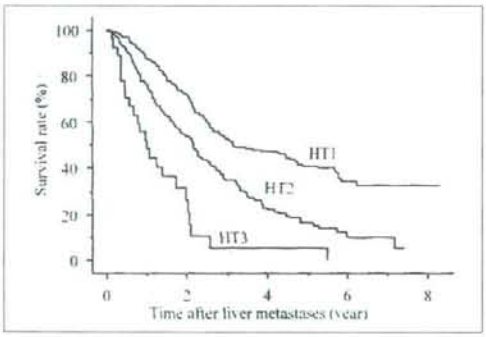

FIGURE 1 Survival curve after liver metastases according to HT factor. HT1: 4 lesions or less and 5cm or less, HT2: Except for HT1 and HT3, HT3: 5 lesions or more and more than 5cm.

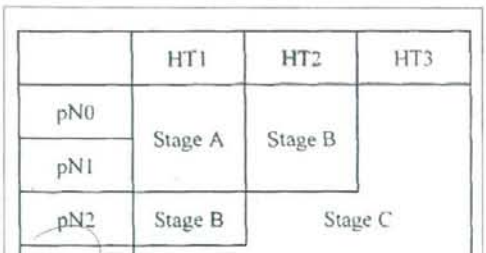

FIGURE 2 A new classification system for liver metastases from colorectal cancer. HT1, ≤4 lesions and ≤5cm; HT2, except for HT1 and HT3; ≥5 lesions and >5cm; EM1, presence of extrahepatic metastases.

(**Figure 2**). Five-year survival rate was 53.5% in Stage A patients, 25.4% in Stage B patients, and 5.8% in Stage C patients. MST was 70.4 months, 31.4 months, and 17.2 months, respectively (**Figure 3**).

Synchronous and Metachronous Liver Metastases

In synchronous cases, 5-year survival was 49.8% in Stage A patients, 25.9% in Stage B patients, and 4.6% in Stage C patients (**Table 6**). MST was 57.3 months, 31.5 months, and 17.1 months, respectively. In metachronous cases, 5-year survival was 57.1% in Stage A patients, 25.0% in Stage B patients, and 8.4% in Stage C patients. MST was 69.4 months, 28.6 months, and 17.9 months, respectively. Furthermore, in synchronous resectable cases, 5-year survival rate was 50.3% in Stage A patients, 33.9% in Stage B patients, and 8.2% in Stage C patients. In metachronous resectable cases, 5-year survival rate was 59.4% in Stage A patients, 28.4% in Stage B patients, and 9.9% in Stage C. In all subgroup, Stage A patients lived significantly longer than Stage B patients ($P<0.0001$), who lived significantly longer than Stage C patients ($P<0.0001$).

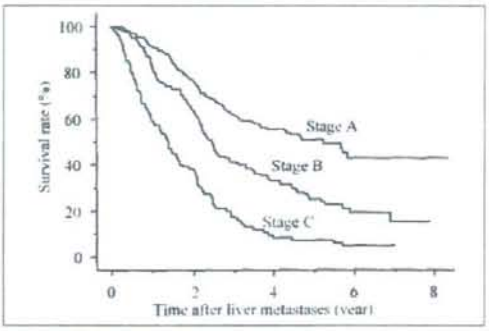

FIGURE 3 Survival curve after liver metastases according to a new classification of liver metastases from colorectal cancer.

TABLE 6 Long-term Survival after Liver Metastases based on Patients Staging

	5-year Survival (%)	Median Survival Time (months)	*P* Value
OVER ALL	30.7	31.4	
Stage A	53.5	70.4	<0.0001
Stage B	25.4	31.4	
Stage C	5.8	17.2	
Synchronous Cases	27.2	30.4	
Stage A	49.8	57.3	<0.0001
Stage B	25.9	31.5	
Stage C	4.6	17.1	
Metachronous Cases	35.7	35.4	
Stage A	57.1	69.4	<0.0001
Stage B	25.0	28.6	
Stage C	8.4	17.9	
Resectable Cases	36.8	38.5	
Stage A	54.9	70.4	<0.0001
Stage B	31.4	38.5	
Stage C	8.9	24.6	
Synchronous Cases	34.7	37.1	
Stage A	50.3	70.4	<0.0001
Stage B	33.9	38.5	
Stage C	8.2	24.8	
Metachronous Cases	39.4	40.5	
Stage A	59.4	-	<0.0001
Stage B	28.4	40.4	
Stage C	9.9	20.5	

DISCUSSION

The American Joint Committee on Cancer (AJCC) staging criteria categorize cases of colorectal cancer with liver metastases as stage IV (17). In Japan, a subclassification for liver metastases from colorectal cancer is commonly used (H0: no liver metastasis, H1: metastasis limited to one lobe, H2: some metastases in both lobes [≤4 lesions], H3: numerous metastases in both lobes [≤5 lesions]) (18). However, all patients with liver metastasis are classified as stage IV. The 5-year survival rate of patients with colorectal cancer with liver metastases ranges from 26% to 51%, yet no classification system is available for these patients. Clearly a need exists for a classification system for patients with colorectal cancer with liver metastases.

Many authors have reported prognostic factors for colorectal cancer liver metastases, including primary tumor stage (4,6,9,12-14,19), number of liver metastases (4,5,7-9,11-14,17,20), maximum size (4-6,7,9), carcinoembryonic antigen (CEA) level (4,5,7-9,16,20), time to liver metastases (5,9,13,14), and extrahepatic disease (7,8,12). Moreover, some investigators developed a scoring system for colorectal cancer liver metastases (4,8,10,14,20). However, none of these systems are available clinically, because of their complexity. During the last decade, more than 2500 articles on colorectal cancer with liver metastases have been published and appear on Medline. It is necessary to establish a common classification system to compare data across different studies.

Table 7 shows large studies for colorectal cancer with liver metastases. Hughes *et al.* listed prognostic factors, including positive mesenteric node in the primary tumor, the time to metastases, size of liver metastases >8cm, number of lesions >2, bilobar metastases, surgical margin >1cm, CEA level, and absence of chemotherapy (5). Nordlinger *et al.* proposed a prognostic scoring system based on seven factors: age older than 60 years, extension into serosa of the primary tumor, lymphatic spread of the primary tumor, size of the largest metastasis >5cm, disease-free interval >2 years, number of liver nodules >4, and resection margin >1cm (4). Scheele *et al.* proposed the following prognostic factors: the presence of satellite metastases, primary tumor grade, the time of metastasis diagnosis, diameter of the largest metastasis, anatomic *versus* nonanatomic approach, year of resection, and mesenteric lymph node involvement (9). Fong *et al.* attempted to score clinical risk

based on five factors: positive mesenteric lymph node in the primary tumor, disease-free interval >1 year, number of liver metastases >1, maximum size of liver metastases >5cm, and CEA level >200ng/mL (10). Although the more prognostic factors we incorporate into a classification system, the better the stratification will be, using too many variables will make the system too complicated. It is important that the classification is simple like the TNM classification system (17). The current classification system in this study incorporates four factors: lymph node metastases in the primary tumor, size of the largest liver metastasis, number of liver metastases, and extrahepatic disease, all of which are easy to remember. Moreover, it represents the prognosis of colorectal cancer liver metastases in synchronous and metachronous cases.

Past studies have reported that mesenteric lymph node metastases are one of the prognostic factors for colorectal cancer with liver metastases (4,9,10,13,14). Most authors investigated the presence or absence of primary lymph node metastases. We investigated the number of mesenteric lymph node metastases of the primary tumor. Although there was no significant difference between pN0 patients (no lymph node metastasis) and pN1 patients (1 to 3 metastases), pN2 patients (≤4 metastases) had a poor prognosis in terms of liver metastases. These findings suggested that pN0 and pN1 patients have an equivalent prognosis in terms of liver metastases. Thus, we drew the line between three and four lymph node metastases.

Though controversy exists (8,12,20), previous reports of large series have proposed the maximum diameter of the liver metastasis as a prognostic factor (4,5,9,10). From our experience, we agree that the largest liver metastasis is an independent prognostic factor. Moreover, we found the best point to draw the line at 5cm of maximum size.

The number of liver metastases has been reported by many authors to be a significant prognostic factor (4,5,6,8,10-12,14,19,20,21-24). Some have reported a significant difference between single and multiple lesions (6,10,12,21,22), and some have demonstrated poor prognosis for patients with ≥4 lesions (4,8,11,12,19,23,24). In our series, we examined the best point to draw the line. Our results indicated that the best point to draw the line was between ≤4 lesions and ≤5 lesions.

Extrahepatic disease has been demonstrated as a negative prognostic factor by many investigators (5,8,9,10). It is unlikely that patients with extrahepatic disease survive more than 5 years. However, according to Scheele *et al.*, curative resection of liver metastases with pulmonary metastases or local recurrence may prolong survival (25). However, in cases with other site recurrences, such as adrenal metastasis, omental deposit, nodules on the surface of the small bowel, and limited peritoneal spread, early recurrence has always resulted even though curative resection was accomplished. Beckurts *et al.* reported poor prognosis of hepatic hilum lymph node metastases. Hence, hilum lymph node metastases are included in extrahepatic disease (26).

TABLE 7 Past Published Large-sized Studies for Liver Metastases from Colorectal Cancer

	Patient number	Primary stage	Liver Size	Metastases Number	Extrahepatic metastases
Hughes, 1968	856	Y	Y	Y	Y
Nordlinger, 1995	1568	Y	Y	Y	-
Sheele, 1995	469	Y	Y	N	Y
Fong, 1999	1001	Y	Y	Y	Y
Current Study	478	Y	Y	Y	Y

Y, independent factor; N, not independent factor; -, not studied.

Although some patients have liver metastases at the time of diagnosis for primary colorectal cancer, others develop liver metastases metachronously. Our classification was suitable for either synchronous or metachronous liver metastases. To this date, no author has reported the classifications which are useful for both synchronous cases and metachronous cases.

This classification of liver metastases from colorectal cancer is not only simple but also useful for retrospective data in most institutes. Until now, there has been no classification system for liver metastases from colorectal cancer that can be used by all authors. Henceforth, we will be able to compare data from various studies and obtain new findings. Additionally, present study could be used to help make treatment decisions for patients with liver metastases from colorectal cancer.

Present classification was developed by retrospective data from limited institutions in Japan. Larger studies are necessary to prove the validity of our classification system.

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APPENDIX

The following institutions and investigators participated in the Study for Establishing Treatments for Hepatic and Pulmonary Metastases from Colorectal Cancer. They are listed in order of the number of cases recruited.

Aichi Cancer Center, Aichi: T Kato, Y Arai, M Suyama, H Nakanishi; Tokyo Metropolitan Komagome Hospital, Tokyo: T Mori, Y Nishimura; Tokyo Medical and Dental University, Tokyo: K Sugihara; National Defense Medical College, Saitama: H Mochizuki; National Cancer Center Hospital, Tokyo: J Yamamoto, H Kondo, T Akasu; Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka: M Higashiyama, M Kameyama; National Kyushu Cancer Center, Fukuoka: S Kohnoe; International Medical Center of Japan, Tokyo: Y Ishizaka; Nagoya

National Hospital, Aichi: M Kataoka; Osaka National Hospital, Osaka: Y Hasuike; Nara Medical University, Nara: S Nakajima; Tokyo Women's Medical University, Tokyo: S Kameoka; Kurume University, Fukuoka: Y Ogata; Kinki University, Osaka: K Okuno; Cancer Institute Hospital, Tokyo: S Okumura; Tokyo University, Tokyo: M Kawahara; Tokyo Metropolitan Bokuto Hospital, Tokyo: N Umekita; NTT West Osaka Hospital, Osaka: K Higashino; Hamamatsu University School of Medicine, Aichi: S Suzuki; Keio University, Tokyo: M Watanabe.

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ORIGINAL CONTRIBUTION

Negative Serum Carcinoembryonic Antigen has Insufficient Accuracy for Excluding Recurrence from Patients with Dukes C Colorectal Cancer: Analysis with Likelihood Ratio and Posttest Probability in a Follow-Up Study

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PURPOSE: This study was designed to determine the efficacy of carcinoembryonic antigen (CEA) monitoring for screening patients with colorectal cancer by using posttest probability of recurrence.

METHODS: For this study, 348 (preoperative serum CEA level elevated: CEA+, n=119; or normal: CEA−, n=229) patients who had undergone potentially curative surgery for colorectal cancer were enrolled. After five-year follow-up with measurements of serum CEA levels and imaging workup, posttest probabilities of recurrence were calculated.

RESULTS: Recurrence was observed in 39 percent of CEA+ patients and 30 percent in CEA− patients, and CEA levels were elevated in 33.3 percent of CEA+ patients and 17.5 percent of CEA− patients. With obtained sensitivity (68.4 percent, CEA+; 41 percent, CEA−), specificity (83 percent, CEA+; 91 percent, CEA−) and likelihood ratio (test positive: 4.0, CEA+; 4.4, CEA−; and test negative: 0.38, CEA+; 0.66, CEA−), posttest probability given the presence of CEA elevation in the CEA+ and CEA− was 72.2 and 65.5 percent, respectively, and that given the absence of CEA elevation was 20 and 22.2 percent, respectively.

CONCLUSIONS: Whereas postoperative CEA elevation indicates recurrence with high probability, a normal postoperative CEA is not useful for excluding the probability of recurrence.

KEY WORDS: Carcinoembryonic antigen; Recurrence; Posttest probability; Likelihood ratio; Sensitivity.

The postoperative surveillance of patients with colorectal cancer is a controversial issue. It is difficult for clinicians to choose the most suitable methods among the many that are available. To date, many reports have focused on the most appropriate methods to choose and when they should be applied, so that cancer recurrence can be detected more effectively.[1,2]

Carcinoembryonic antigen (CEA) is a cell surface glycoprotein that is produced by 90 percent of colorectal cancer[3,4] and that contributes to the malignant characteristics of the tumor. Quantitative measurements of serum CEA can be performed easily, and CEA is commonly used as a marker of colorectal cancer recurrence.[5–7] The level of CEA has been reported to correlate with the stage of colorectal cancer, and its correlation with liver metastasis is reportedly better than that with recurrent disease in other locations.[7,8] To detect colorectal cancer recurrence, ultrasonography, computed tomography,[9] chest x-ray examination, and, most recently, FDG-PET (2-[^{18}F] Fluoro-2-deoxy-D-glucose positron emission tomography) have been used,[10] other biologic tumor makers have appeared,[11] but no modality is more useful than CEA.[12–15] Despite the widespread use of CEA during follow-up, there are still some unresolved issues about its effectiveness as a preoperative and postoperative marker. One issue is how accurately elevated CEA detects recurrence of colorectal cancer and another is whether postoperative CEA elevates when recurrence occurs in patients with negative preoperative CEA. Therefore, it is still a matter of debate whether clinicians can rely solely on CEA for the follow-up of patients with colorectal cancer. Previous studies based on sensitivity and specificity have not made this clear. On the other hand, sensitivity and specificity can be combined into one measure called likelihood ratio. Likelihood ratio provides a summary of how many times more (or less) likely patients with the disease are to have that particular result than patients without the disease, and it also can be used to calculate the probability of disease for individual

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patients (posttest probability). For these reasons, likelihood ratio is becoming increasingly popular for reporting the usefulness of diagnostic tests.[16]

This study was designed to evaluate the accuracy and efficacy of measuring serum CEA value in Dukes C by using likelihood ratio and posttest probabilities.

PATIENTS AND METHODS

A total of 680 patients underwent potentially curative surgery for colorectal cancer between December 1990 and December 2000 at Aichi Cancer Center Hospital. Of these patients, 417 (219 men, 198 women) were histologically proven to have lymphatic metastasis (Dukes C). Patients with multiple cancers (50 patients), insufficient examinations (12 patients), persistent CEA elevation after surgery (3 patients), and squamous-cell carcinoma (4 patients) were excluded. The remaining 348 patients with Dukes C were enrolled in this retrospective study. The population characteristics are summarized in Table 1. All patients underwent measurement of the preoperative serum CEA level and were classified as elevated (CEA+, n=119) or normal (CEA−, n=229). The mean preoperative serum CEA level was 9.3±20.8 (range, 0–245) ng/ml. In this study, a serum CEA value of 5 ng/ml or higher was considered to represent CEA elevation. All patients were followed for more than five years or until death with routine serum CEA examination every three months. Ultrasonography and/or computed tomography and chest x-ray examinations were performed every three to six months. Additional imaging was performed in patients with elevated postoperative CEA levels to determine whether recurrence was present.

Table 1.

Variable	*Patients*
Age (yr) (mean ± SD)	60.6±11.1
Male/female ratio	178/170
pT category	
t1	18
t2	59
t3	232
t4	39
Pathologic type	
Well	27
Moderate	291
Mucinous	10
Poor	20
Location	
Colon	160
Rectum	188
Preoperative CEA value (mean ± SD)	9.3±20.8

SD=standard deviation; pT=pathologic tumor stage.

Statistical Analysis

All patients of the two groups (CEA+, 119; CEA−, 229) were randomly assigned into two subgroups (patients for calculating likelihood ratio, LR, and those for calculating pretest probability, PP) according to the statistical random table. LR were further classified into four groups according to presence or absence of recurrence and an elevated or normal CEA value (Fig. 1): true positive (positive recurrence and CEA elevation); false positive (negative recurrence and CEA elevation); false negative (positive recurrence and normal CEA); and true negative (negative recurrence and normal CEA). Sensitivity was calculated as true positive/(true positive + false negative), and specificity was calculated as true negative/(true negative + false positive). From these values, we calculated the sensitivity, specificity, likelihood ratio, and posttest probabilities of recurrence.

The likelihood ratio given a positive test result (LR+) is defined as the probability of a patient with disease having a positive test divided by the probability of a patient without disease having a positive test. Thus, the LR+ was calculated as the sensitivity/(1 − specificity). And that given a negative result (LR−) is as the probability of a patient with disease having a negative test divided by the probability of a patient without disease having a negative test. The LR− was calculated as (1 − sensitivity)/specificity. The posttest probability calculated with the likelihood ratio and the pretest probability. In this study, the posttest probability was obtained from the following formula:

$$\text{Pretest odds} = \text{pretest probability} / (1 - \text{pretest probability}) \quad \text{(Formula 1)}$$

$$\text{Posttest odds} = \text{pretest odds} \times \text{likelihood ratio} \quad \text{(Formula 2)}$$

$$\text{Posttest probability} = \text{posttest odds} / (1 + \text{posttest odds}) \quad \text{(Formula 3)}$$

Pretest probabilities of recurrence were determined by using the incidence of recurrence based on PP (CEA+, 59; CEA−, 115). In this study, accuracies for each recurrent site in CEA+ and CEA− also were evaluated with positive and negative predictive values (PPV and NPV) using 119 and 229 patients, respectively.

RESULTS

Pretest Probability

Follow-up of patients in PP revealed recurrence in 23 (39 percent) of the 59 CEA+ patients and 35 (30.4 percent) of the 115 CEA− patients (Fig. 1; Table 2). From these

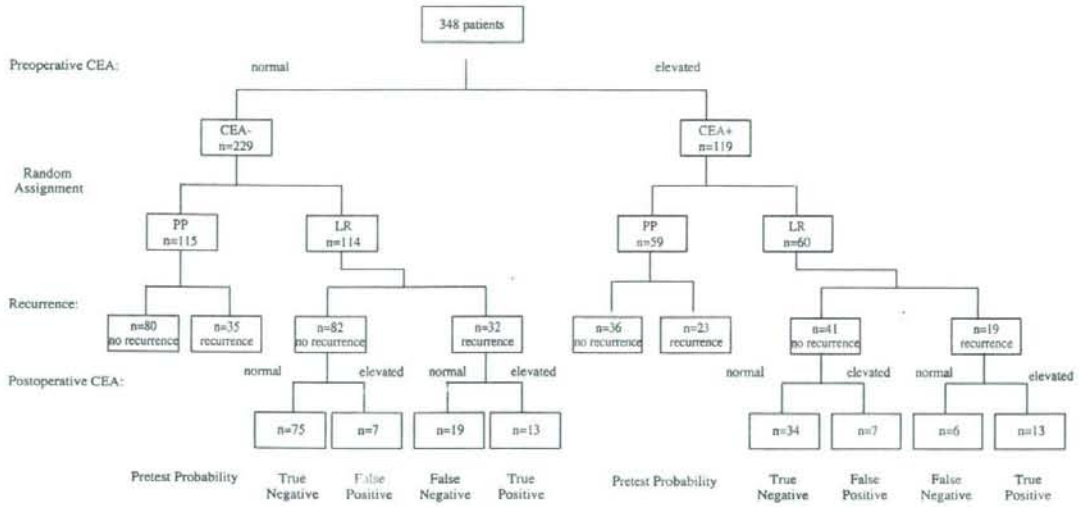


FIGURE 1. Patient classification. All 348 patients were divided into two groups according to the preoperative carcinoembryonic antigen (CEA) value: CEA+ (n=119) and CEA− (n=229). They were further divided into two groups: patients for pretest probability: PP (CEA+, n=59; CEA−, n=115) and those for likelihood ratio: LR (CEA+, n=60; CEA−, n=114). LR was divided into four groups according to presence or absence of recurrence and CEA elevation: LR=group for calculating likelihood ratio; PP=group for calculating pretest probability.

values and Formula 1, pretest odds were calculated (CEA+, 0.64; and CEA−, 0.43; Table 2).

Likelihood Ratio

During follow-up of LR patients, 19 (31.7 percent) of 60 CEA+ patients and 32 (28.1 percent) of 114 CEA− patients developed recurrence (Fig. 1). In this study, 43 of 109 (PP: 58 and LR: 51) patients were diagnosed histologically, and the remaining 66 patients radiologically. Of these LR patients with recurrence, CEA elevation (true positive) was seen in 13 CEA+ and 13 CEA− patients, and no CEA elevation (false negative) was seen in 6 and 19 patients, respectively. CEA elevation without recurrence (false positive) was seen in seven CEA+ and seven CEA− patients. True negative results (no recurrence and no elevation of CEA) were seen in 34 CEA+ and 75 CEA− patients (Fig. 1; Table 3).

Using these data, for recurrence, postoperative CEA had a sensitivity of 68.4 percent in CEA+ patients and 41 percent in CEA− patients, and a specificity of 82.9 percent and 91 percent, respectively. Using these results, the positive likelihood ratio for recurrence was 4.0 for CEA+ patients and 4.4 for CEA− patients, and the negative likelihood ratio was 0.38 and 0.66, respectively (Table 3).

Posttest Probabilities

Posttest odds were obtained by multiplying the pretest odds and the likelihood ratio. Thus, the posttest probabilities of CEA+ and CEA− patients given the presence of CEA elevation were 72.2 and 65.5 percent, respectively, and the negative posttest probabilities given the absence of CEA elevation were 20 and 22.2 percent, respectively (Fig. 2; Table 3). When the postoperative CEA level was elevated, probabilities of recurrence in CEA+ and CEA−

Table 2. Outcome and primary sites of recurrence of LR patients with CEA+ and CEA− postoperative serum levels

	CEA+				CEA−			
	LR (n=60)		*PP (n=59)*		*LR (n=114)*		*PP (n=115)*	
No recurrence	41	(68.3)	36	(61.0)	82	(71.9)	80	(69.6)
Recurrence	19	(31.7)	23	(39)	32	(28.1)	35	(30.4)
Liver	9	(15)	7	(11.9)	13	(11.4)	13	(11.3)
Local	6	(10)	8	(13.6)	6	(5.3)	8	(7)
Lung	4	(6.7)	7	(11.9)	11	(9.6)	14	(12.2)
Peritoneum	0	(0)	2	(3.4)	2	(1.8)	2	(1.7)
Lymph node	5	(8.3)	3	(5.1)	3	(2.6)	3	(2.6)
Hematologic	0	(0)	0	(0)	2	(1.8)	1	(1.7)

CEA=carcinoembryonic antigen; LR=group for likelihood ratio; PP=group for pretest probability. • Data are numbers with percentages in parentheses.

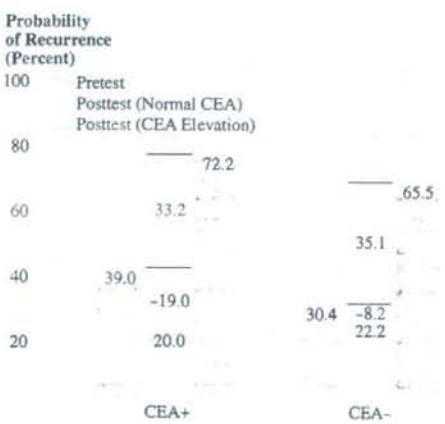
Table 3.

	CEA+ (n=61)	*CEA− (n=114)*
Sensitivity	0.68	0.41
Specificity	0.83	0.91
Likelihood ratio (test-positive)	4.0	4.4
Likelihood ratio (test-negative)	0.38	0.66
Pretest probability (%)	39.0	30.4
Posttest probability (test-positive) (%)	72.2	65.5
Posttest probability (test-negative) (%)	20.0	22.2

CEA=carcinoembryonic antigen. • Likelihood ratio (test-positive) = sensitivity/(1 − specificity); • Likelihood ratio (test-negative) = (1 − sensitivity)/specificity; • Posttest probability = posttest odds/(1+ posttest odds); • Posttest odds = pretest odds x likelihood ratio.

patients were increased from the pretest probabilities by 33.2 percent (pretest probability 39 percent; posttest probability 72.2 percent), and 35.1 percent (pretest probability 30.4 percent; posttest probability 65.5 percent), respectively. However, even when postoperative CEA remained at a normal level, the probabilities of recurrence were decreased from the pretest probabilities by only 19 percent (posttest probability 20 percent) in CEA+ patients and 8.2 percent (posttest probability 22.2 percent) especially in CEA− patients, respectively (Table 4).

FIGURE 2. Probabilities of recurrence according to postoperative carcinoembryonic antigen (CEA) in CEA+ and CEA− patients. Pretest probabilities, CEA elevation, and negative posttest probabilities of recurrence according to each site in CEA+ and CEA− patients. Whereas posttest probabilities of CEA elevation were high as approximately 70 percent (CEA+, 72.2 percent; CEA−, 65.5 percent), those of Normal CEA were approximately 20 percent (20 percent, CEA+; 22.2 percent, CEA−), which were almost same as pretest probabilities. In CEA− patients, normal CEA decreased the probability of recurrence only 8.2 percent from pretest probability.



Accuracy of CEA Measurement for Each Site of Recurrence in CEA+ and CEA− Patients

The accuracy of serum CEA measurement for each site of recurrence in CEA+ and CEA− patients was evaluated with PPV and NPV (Table 4). In both CEA+ and CEA− cases, PPV of liver metastasis was relatively high (33.3 and 25, respectively) compared with other sites of recurrence. In contrast, PPV of lung metastasis was low, especially in CEA− cases (PPV, 5.0).

DISCUSSION

Despite the widespread use of monitoring serum CEA value in colorectal cancer patients, its accuracy and efficacy is still unclear.[14,17] Goldberg *et al.*[18] documented that approximately 40 percent of curative resections are performed for recurrent disease after discovery by CEA elevation. However, many reports have discussed the merits of serum CEA as a marker of colorectal cancer recurrence,[7,8,19–21] whereas others have questioned its value,[22] especially in patients with normal preoperative CEA levels.[23] Thus, it also is uncertain whether measurement of CEA alone is enough when monitoring patients with colorectal cancer. One possible reason of this uncertainty is that previous studies were based on sensitivity and specificity.[7,8,19–21] There exists a difference in survival rate between preoperatively CEA− and CEA+ patients,[24,25] so in terms of recurrence, morbidity rate of CEA+ and CEA− patients is different. It is difficult to compare the accuracy of the test with sensitivity and specificity when the morbidity rate is different.[26–28] Recently, an increasing number of investigators have evaluated the efficacy of diagnostic methods by using the likelihood ratio,[29,30] which is reported to be superior to sensitivity and specificity for this purpose. The likelihood ratio is less influenced by morbidity rates than sensitivity and specificity and allows posttest probabilities to be obtained from pretest probabilities.[26–28] In this study, the likelihood ratio and posttest probability gave us more obvious information about efficacy of CEA monitoring. The probability of recurrence is expected to increase more or decrease less as a result of the examinations. However, these results show that whereas postoperative CEA

Table 4.

	Liver	*Lung*	*Local*	*Peritoneum*	*Lymph node*
CEA+					
PPV	33.3	14.3	23.8	9.5	19.0
NPV	92.5	97.5	97.5	97.5	97.5
CEA−					
PPV	25.0	5.0	10.0	10.0	15.0
NPV	91.5	89.4	96.8	98.9	98.9

CEA=carcinoembryonic antigen; PPV=positive predictive value; NPV=negative predictive value.

elevation indicates recurrence with high probability, a normal postoperative CEA level is not useful for excluding the probability of recurrence, which is especially common in patients without preoperative CEA elevation. Normal postoperative CEA in CEA− patients results in only decreasing 8.2 percent of probability of recurrence from pretest probability (Fig. 2). This suggests that it is necessary to rule out recurrence with other examinations even if postoperative CEA is normal.

In terms of recurrence site, it has been thought that serum CEA surveillance is useful for detection of liver metastases but not useful for detection of local recurrence or other types of metastasis.[7,8,31–33] In the present study, whereas postoperative CEA elevation predicted liver metastasis with high reliability in both CEA+ and CEA− cases, it had a lower positive predictive value for lung metastasis, especially in CEA− patients, than for other sites of recurrence.

As imaging workup techniques continue to improve and new, more effective chemotherapies appear,[34,35] intensive postoperative surveillance is needed. Use of the likelihood ratio and posttest probability revealed that CEA elevation has modest power to detect colorectal cancer recurrence regardless of the preoperative CEA value. However, whereas CEA had modest power for detecting recurrence, it was insufficient to rule out patients without recurrence even if they had normal postoperative CEA values. This result shows that surveillance of patients with colorectal cancer by measurement of CEA alone is insufficient and additional imaging is necessary even though serum CEA value is normal.

CONCLUSIONS

Use of the likelihood ratio and posttest probability has revealed that CEA elevation has modest power to detect colorectal cancer recurrence, irrespective of the preoperative CEA value. However, it does not allow a conclusion to be made about absence of recurrence even if the CEA level is normal, especially in patients who are CEA− preoperatively. Our findings suggest that another parameter, in addition to the serum CEA level, is absolutely essential when postoperatively monitoring patients with colorectal cancer.

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骨盤内手術—出血防止の工夫と出血時の対応—

愛知県がんセンター中央病院消化器外科

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手術の tips and pitfalls

骨盤内手術―出血防止の工夫と出血時の対応―

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キーワード　直腸癌，骨盤内出血，仙骨前静脈叢，neurovascular bundle，thumbtack

I. はじめに

直腸癌手術における骨盤内操作では，深い層に切り込み，あるいは再発時には瘢痕内での操作のため，仙骨前静脈叢や内腸骨静脈損傷による大量出血をみることがある．骨盤内静脈の血流量は豊富であり，剝離面の最深部で出血するため，あっという間に術野が血の海となってしまう．この様な出血をきたさないためには，骨盤内の臨床解剖[1]をよく理解し，適切な手技を行うことが大事であり，もし出血した場合も対応策を習得している必要がある．

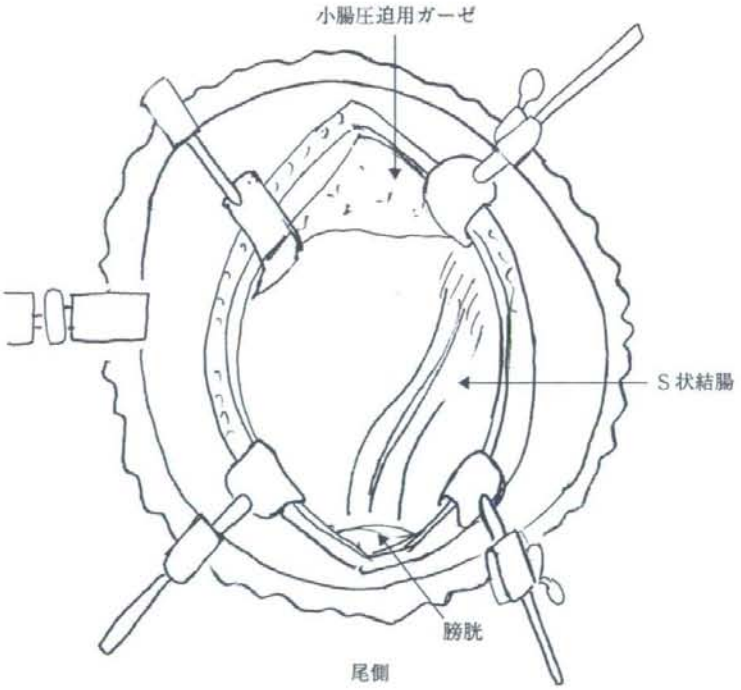

図1　良好な手術視野の確保が必要
我々はできるだけ良い視野を保つため，1. Bookwalter retractor（図）2. 下肢を水平位にした截石位　3. headlight system　4. 骨盤腔用の特注鉤を使用している．

HOW TO PREVENT AND CONTROL MASSIVE BLEEDING DURING PELVIC RECTAL OPERATION
Takashi Hirai and Tomoyuki Kato
Department of Gastroenterological Surgery, Aichi Cancer Center Hospital, Aichi, Japan

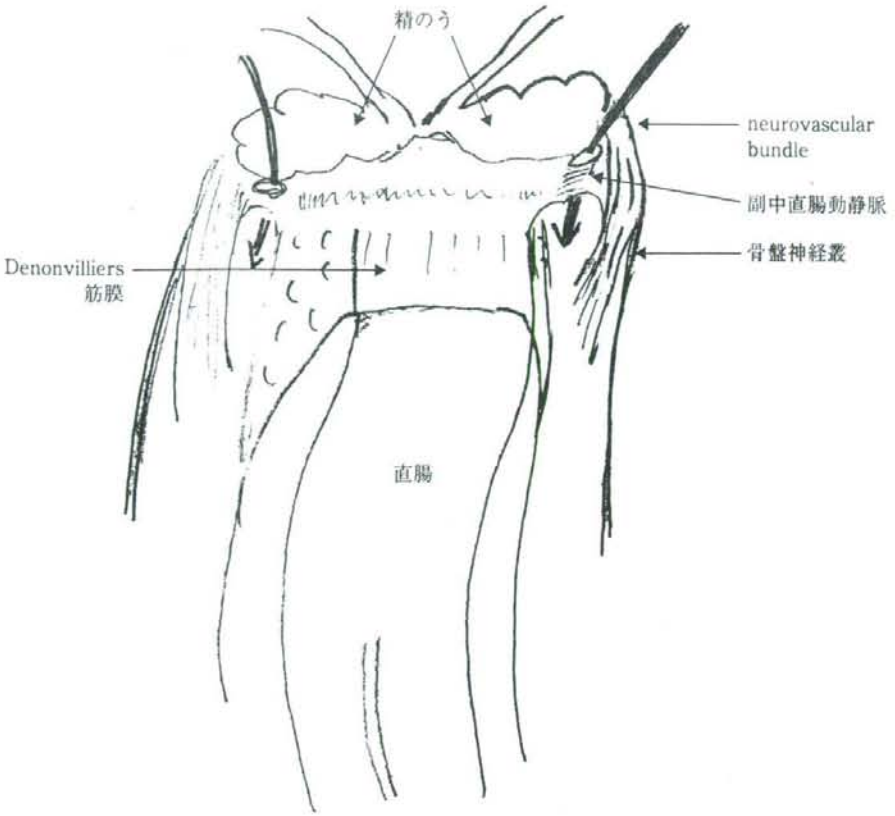

図2　初回手術時の出血（neurovascular bundle）
初回手術時に骨盤内で出血しやすい部位のひとつは，neurovascular bundle である．これは Denonvilliers 筋膜の前立腺・膣側と密着している．剝離時その静脈から出血しやすい．また，直腸間膜との連絡枝（副中直腸動静脈）がよく存在し，本筋膜の切除の有無に関わらず，その存在を確認し，vessel sealing system あるいは超音波切開凝固装置で切離する．

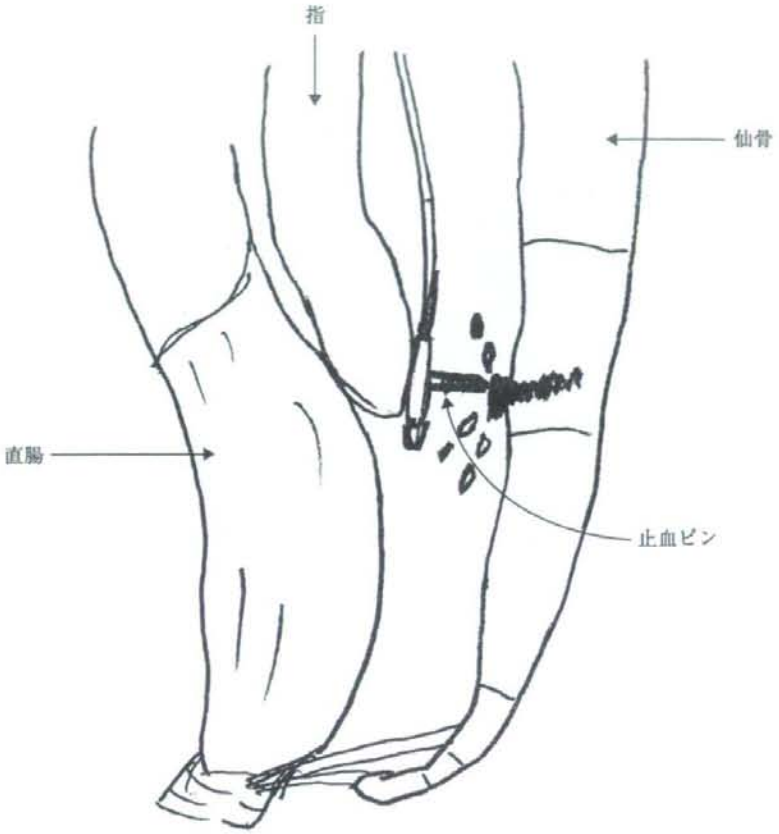

図3　初回手術時の出血（仙骨前静脈叢）
第3から5仙骨前面の椎体静脈叢との太い連絡枝（仙骨前静脈叢）を誤って傷つけた場合，通常の止血操作ではコントロールできなくなる．このような場合，まずパッキングを行い，thumbtack（止血ピン：チタン製が市販されている）をapplierを使用して止血点に押し込む[2]，あるいは腹直筋などの一部を出血部にあてがい，その上から電気メスにて，凝固する[3]．

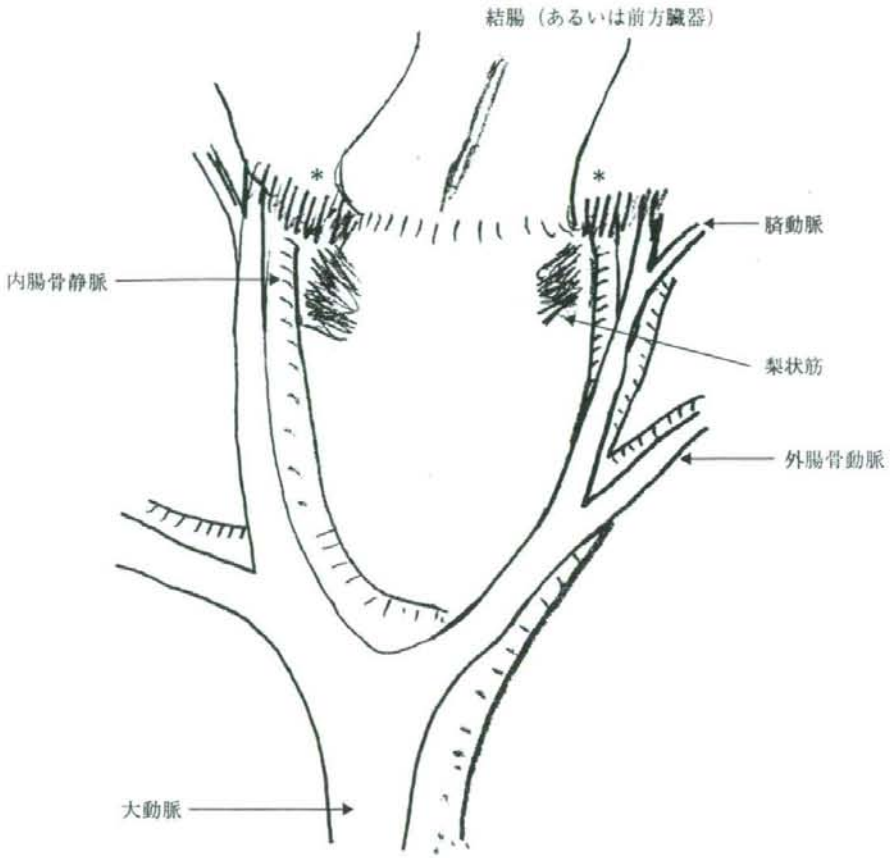

図4　骨盤内再発手術時の出血点
再発手術の際には，仙骨前面から内腸骨血管にかけては瘢痕が強く，仙骨前静脈叢からの出血は，おこりやすい．再発手術時には必ず，thumbtack は準備しておく．また，仙骨の両側では必ず，内腸骨静脈が存在し，瘢痕に埋もれている．特に梨状筋を超えるあたり（アスタリスク）で内腸骨静脈を損傷しやすい．

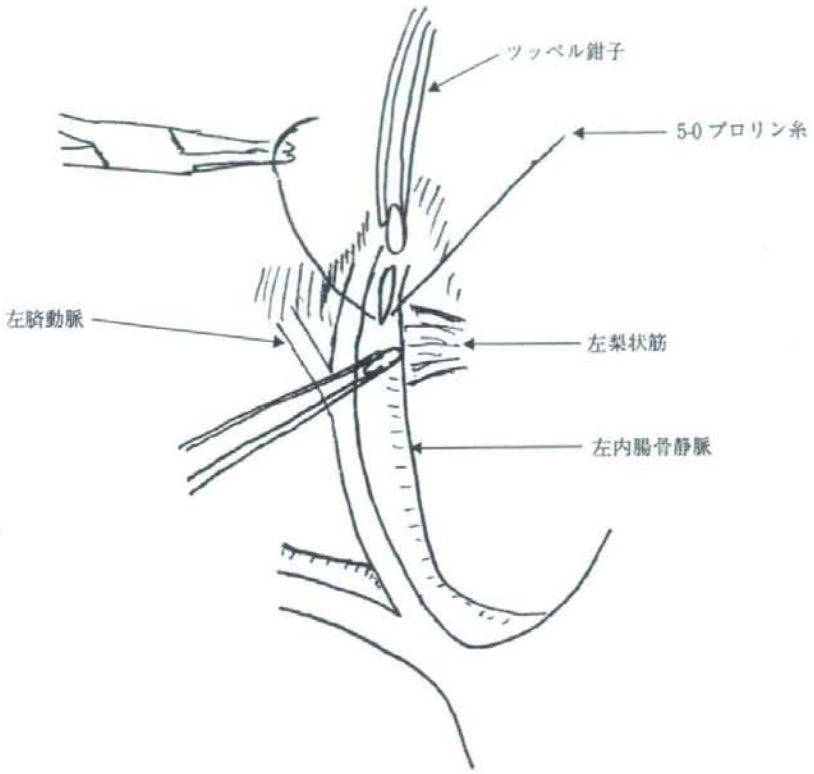

図5　骨盤内再発手術時止血操作（内腸骨静脈損傷）
一旦，術野の奥底で内腸骨静脈の枝あるいは本幹を損傷した場合，指あるいはツッペル鉗子で出血点をおさえながら，周囲の剝離を行い，術野を確保する．多くは内腸骨静脈が縦に裂けているため，ツッペル鉗子で静脈の前後を圧迫して裂傷部を確認しながら5-0 プロリン　SH1 の針で 23cm 以上の長さの持針器で血管を縫合する．

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4. 直腸癌のD2，D3郭清の要点

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はじめに

大腸癌の診断・治療を標準化(stagingだけでなく，治療内容の規定も目的)するために，大腸癌研究会によって『大腸癌取扱い規約』(現在第7版[1])が提示されてきた。理念を優先した規約ではあるが，根治性を重視する一貫した姿勢が保たれている。直腸癌においては，下腸間膜動脈根部リンパ節，側方リンパ節を遠隔リンパ節とせず，郭清対象としてきた。また，肛門側切除距離も具体的な数値を示し，臨床医にとっての実臨床のより所となってきた。2005年，大腸癌研究会により『大腸癌治療ガイドライン』[2]が作成され，その根拠となるデータや文献が紹介されるにあたっては，記載の統一や治療の方向性を示した『大腸癌取扱い規約』の果たした役割が大きい。一方，国際的には『大腸癌取扱い規約』と同様の目的をもったものとしてUICC-TNM分類があるが，ガイドライン的な内容はない。NCIのguideline 2000[3]，PDQ (http://cancernet.nci.nih.gov/pdq.html)は治療指針であるが，とくに直腸癌におけるリンパ節郭清の役割に関しては，『大腸癌取扱い規約』との相違が大きく，将来的にはevidenceを基にしてこの溝を埋めていく必要がある。すでに側方リンパ節予防的郭清については，JCOG-0212の臨床試験が進行中である。本稿では『大腸癌取扱い規約』第7版に従い，『大腸癌治療ガイドライン』に沿って，直腸癌(RSを除く)に対する標準的リンパ節郭清について当院でのデータ(1965～1999年)も示しながら解説する。

直腸癌リンパ節郭清の基本

A. 『大腸癌治療ガイドライン』

総括的に深達度によって郭清の程度を分け，SMはD2(傍腸管と中間リンパ節郭清)，MPはD2あるいはD3(領域リンパ節郭清)，筋層を貫くものはD3を勧めている。以下，中枢・側・傍腸管方向に分ける。

1)　中枢方向

深達度による当院での直腸癌リンパ節転移率は，表1[4]のごとくで，pMPまでNo.253への転移はなかったが，筋層を貫くと4.5%に転移を認めた。そして，転移例の5年生存率は約40%であった。側方転移郭清例とほぼ同様の生存率であった。SMでのNo.253郭清は必要ないが，深達度の術前術中診断が確実でないことや252リンパ節郭清を確実にするために，MPから253郭清は行う。

2)　側方向

第6版までは側方郭清がなければ，どんなに直腸間膜を切除し，腸管傍リンパ節，中間リンパ節を郭清してもRaではD2，Rb，PではD1にしかならない厳しい基準であった。第7版からは直腸(RSは除く)では側方郭清がなくても，腸管傍リンパ節と中間リンパ節が郭清されていればD2とされ側方郭清の重みが実臨床に近づいた。ガイドラインでは側方郭清の効果を解説しており，筋層を貫くもの，そして，腫瘍下縁が腹膜反転部より肛門側にかかるものに対象を絞ると，側方リンパ節転移が20.1%に存在すること，そして側方郭清に

表1　上方向リンパ節転移率

部位	pSM	pMP	pSS，SE，A
252	2/72 (2.8)	6/170 (3.8)	56/223 (25)
253	0	0	10/223 (4.5)

( )：%