Table 3. Independent risk factors for second primary cancer (multivariate logistic regression analysis)

Factor	Odds ratio	95% CI	p value
Age	1.345	1.126–1.686	0.0245
Male sex	1.980	0.890–4.405	0.0938
Tumor site			
Left-side colon	2.320	0.833–6.452	0.1076
Rectum	1.167	0.358–3.802	0.7986

Table 4. Frequency of the second primary cancer according to the age of patients

Age	Second primary cancer +	Second primary cancer –	Total
<50	4	37	41 (9.8%)
50–60	4	95	99 (4.0%)
60–70	21	87	108 (19.4%)
>70	9	44	53 (17.0%)

Table 5. Comparison of the observed incidence and expected incidence calculated using the Osaka Cancer Registry data

	Observed incidence	Expected incidence	O/E ratio	95% CI	p value[1]
Overall	40	15.4	2.6	1.857–3.542	<0.01
Lung	8	2.5	3.2	1.379–6.299	<0.01
Stomach	8	3.0	2.7	1.164–5.315	<0.05
Liver	6	2.2	2.7	0.989–5.882	NS

[1] Poisson distribution analysis.

cer. The patients with a second primary cancer were older at the time of surgery than those without a second primary cancer ($p = 0.0049$). Tendencies concerning the gender and tumor site were observed; however, no statistically significant difference was found ($p = 0.0713$ and $p = 0.0896$, respectively).

Thereafter, the clinicopathological characteristics that may influence the second primary cancer were investigated using a multivariate analysis (table 3). For a multivariate analysis, we selected the variables for which p value was less than 0.1 by univariate analysis. A logistic regression analysis revealed that age was an independent risk factor for second primary cancer in patients with CRC after a curative resection with an odds ratio of 1.345 (95% confidence Interval, CI: 1.126–1.686, $p = 0.0245$). Sex and tumor site were not independent risk factors.

Frequency of the Second Primary Cancer according to the Age of Patients

We investigated the risk of metachronous second primary cancer according to age (table 4). The frequency of second primary cancer was not so high in younger patients (less than 60 years old). However, in elderly patients (over 60 years old), the frequency increased from 5.7 to 14.2%.

Comparison of Observed Incidence and Expected Incidence

Data from the Osaka Cancer Registry (Osaka residents, Japan) were used to determine the epidemiological significance of the current findings in comparison with the normal population. The expected incidence of extracolorectal cancers was 15.4 in 301 CRC patients, whereas the observed incidence was 40 in CRC patients (table 5). The O/E ratio was 2.6 for CRC patients, which was statistically significant (95% CI: 1.857–3.542, $p < 0.01$). An investigation of the O/E ratio in each organ revealed that the incidence of lung and gastric cancer in CRC patients was significantly high with O/E ratios of 3.2 and 2.7 (95% CI: 1.379–6.299 and 1.164–5.315, $p < 0.01$ and $p < 0.05$, respectively). However, the O/E ratio for hepatocellular carcinoma did not show statistical significance.

Discussion

A number of population-based studies have focused on second primary cancers occurring after cancers of the colon and rectum [12–15]. The results of these studies are varied and include a significantly increased risk of developing second cancers of the stomach, small intestine, colon, rectum, kidney, bladder, prostate, thyroid, breast, corpus uteri, ovary, brain, and gallbladder. However, the results of these studies are inconsistent regarding second primary malignancies after CRC. A markedly increased risk of developing certain subsequent malignant diseases may also have an impact on the follow-up routines, thereby helping us to better identify the high-risk groups suitable for screening.

Multiple cancers may occur in an individual because of a genetic predisposition, environmental exposure, cancer therapy or immunological deficiency. Due to the

remarkable improvement in cancer treatment, many cancer patients now survive long after treatment. Tsukuma et al. [3] have reported that second primary cancers developed in 5,071 (2.3%) of 217,307 cancer patients among Osaka residents. Because cancers are more likely to develop in either older patients or during a long follow-up period [4], the age at diagnosis of CRC and the duration of the postoperative follow-up period are particularly important factors. Similarly, the incidence of cancer in male patients is higher than that in female patients [4]. In the present study, the CRC patients with a second primary cancer were significantly older at the time of surgery than those without a second primary cancer. However, no significant difference was observed in sex or the follow-up period between the two groups. A logistic regression analysis was employed to exclude the possible influence of these different backgrounds. Only the age was found to be an independent risk factor. This analysis revealed an approximately 1.345-fold increase in older CRC patients (95% CI: 1.126–1.686, p = 0.0245).

It is important to compare identical populations and also evaluate various factors such as ethnic origin and geographic region when comparing the cancer incidence from the registry database with a normal population. The present study, therefore, compared the patients in this hospital with the data of the Osaka Cancer Registry, because these data came from identical populations. The current results demonstrated that CRC patients had a significantly high risk of postoperative second primary cancer. Specifically, the frequency of lung and gastric cancer was significantly high. Distinguishing extracolorectal primary cancers from recurrent CRC may be difficult in some patients. A recurrence of CRC is frequently observed in the liver, lung, and local site [16]. In the current study, postoperative liver cancer was observed in 6 patients with hepatitis-infected CRC. Five patients underwent a surgical resection and the lesion was confirmed histopathologically as hepatocellular carcinoma. Another patient underwent transarterial embolization of the lesion because of hypervascularity, a typical feature of hepatocellular carcinoma. Similarly, all 8 cases of postoperative lung cancer in the present study were solitary lesions, and the lesions were histopathologically confirmed to be primary lung cancer.

HNPCC is known to cause an increased risk of cancers of the corpus uteri, ovary, stomach, pancreas, and small intestine [17, 18]. Therefore, it is a strong candidate for a genetic condition underlying co-occurrence of CRC with these other cancer types. In the current study, nine HNPCC patients were recognized (9/301, 3.0%). However, no statistical difference was observed in the frequency of HNPCC in the CRC patients with or without second primary cancer.

The present data demonstrated that extracolorectal cancer frequently (38 of 301 CRC patients, 12.6%) occurs in various organs including the lung, stomach, and liver. It is well recognized that cancers develop because of accumulated alterations of multiple responsible genes. Cancer-bearing patients are thus assumed to be at increased risk of developing cancers in other organs [3, 15, 19]. The underlying mechanisms of such spread might include environmental factors, unknown infections and genetic abnormalities. The p53 gene is the most frequently altered gene in several human cancers, with mutations reported in 50–75% of CRC, 60% of lung cancer and 50% of gastric cancer. Furthermore, mutations in K-*ras* can also be detected in CRC (35–42%), lung cancer (about 30%), and gastric cancer (8%) [20–23]. However, these genes may not entirely explain the current findings. It is possible that several genes can mutate easily or cannot be repaired in CRC patients. Further studies are required to clarify the underlying mechanisms.

The current data revealed that 38 (12.6%) of 301 CRC patients developed a second primary cancer. Second primary cancers occurred in 29 males (15.3%) among the 301 CRC patients. In contrast, 9 (8.1%) of 111 female CRC patients developed a second primary cancer. In large population-based studies of CRC patients, the second primary cancer risk, excluding CRC, is 3.4–7.7% in males and 2.6–5.6% in females [13, 15, 24]. The current results were higher than the findings of those reports. This difference may be attributed to the follow-up period. In previous studies, the follow-up periods were shorter than our study. Cancers are more likely to develop in older patients or during a longer follow-up period [4]. In fact, in a 95-month follow-up, Yamamoto et al. [25] reported the frequency of multiple primary malignancies to be 17.0% (222/1,304).

In the present study, the total incidence of postoperative extracolorectal cancers in CRC patients was significantly higher than that in the normal population, especially in lung and gastric cancer. In CRC, approximately 80% of all recurrences developed within 3 years after the initial resection and 95% developed within 5 years [16]. As a result, the follow-up for CRC without recurrence is generally stopped at 5 years. The current results also demonstrate that most second primary cancers after a resection for CRC occur within less than 5 years. However, in some patients, the second primary cancer developed after more than 5 years [26]. It is therefore consid-

ered to be very dangerous that postoperative second primary cancer is followed in CRC patients with the same follow-up system as that used for CRC patients with a first primary cancer. CRC patients should be informed of the high risk of a second primary cancer. CRC patients should therefore receive a checkup for extracolorectal cancer within 5 years after the initial diagnosis of CRC. However, some second primary cancers occurred more than 5 years after the initial diagnosis of CRC. Therefore, CRC patients should receive a checkup for extracolorectal cancer not only during the follow-up period of CRC but also after the follow-up period for CRC.

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Postoperative Complications in Elderly Patients With Colorectal Cancer

Comparison of Open and Laparoscopic Surgical Procedures

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Background: Surgery is associated with higher morbidity and mortality rates in elderly patients with colorectal cancer compared with younger patients. The aim of this study was to examine preoperative evaluation for selecting operative procedure in elderly patients with colorectal cancer.

MethodsIn: The study of all patients who underwent open surgery (OS) or laparoscopically assisted surgery (LAS) for colorectal cancer from January 2004 to December 2007 were aged ≥ 71 years. Preoperative evaluation, operative factors, morbidity, and mortality were analyzed by the Physiological and Operative Severity Score for Enumeration of Mortality and Morbidity (POSSUM) and Prognostic Nutritional Index (PNI).

Results: A total of 129 patients were included in this study. Fifty-one patients underwent OS, and LAS was performed on 78 patients. The morbidity rate was 51.3% (40 patients) for the OS group and 23.5% (12 patients) for the LAS group. Three LAS patients (5.9%) subsequently required OS. One LAS patient died postoperatively. There were significant differences in the Operative Severity Score (OSS) in POSSUM and PNI, but not Physiologic Score (PS) in POSSUM, between the two groups. In the OS group, there were significant differences in PS, OSS, and PNI between those with or without complications, whereas in the LAS group, OSS, but not PS or PNI, was significantly lower in those without than in those with complications.

Conclusions: Compared with OS, LAS is associated with a lower incidence of complications in elderly patients with colorectal cancer. The nutritional status correlated with postoperative complications in the OS group.

Key Words: elderly, colorectal cancer, complications, laparoscopic surgery

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The number of operations conducted on elderly patients with colorectal cancer has been increasing with the aging of population and increased prevalence of colorectal cancer in Japan. As it is considered that elderly patients tend to have more than one underlying disease, surgery is associated with higher morbidity and mortality rates in this age group than in the younger age group. On the other hand, there is a certain discrepancy between chronological age and physical age in terms of background factors, such as heart, lung, and renal functions. Age is one of the important factors for preoperative assessment. However, it is necessary to evaluate preoperative conditions precisely for the decision of optimal surgical intervention.

Compared with open surgery (OS), laparoscopically assisted surgery (LAS) is associated with better immune and inflammatory responses, earlier postoperative recovery, similar cancer recurrence rate, and long-term survival.[1–6] Although it was reported that advanced age is not a limiting factor for performing LAS, most of the studies carried out to date are retrospective,[7–14] and thus provide only a limited level of evidence. In addition, the standards of preoperative evaluations, exclusion criteria, and the definition of complications are not systematically organized. In the this study, we examined postoperative short-term outcome, using the Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity (POSSUM)[15] and Prognostic Nutritional Index (PNI)[16] for preoperative evaluation.

PATIENTS AND METHODS

The patients of this study were patients aged 71 years and older who were consecutively scheduled for surgical treatment for colorectal cancer at our department between January 1, 2004 and December 31, 2007. The surgical techniques were applied electively either laparoscopically or through direct standard OS by 5 surgeons who were proficient in both LAS and OS at our department. Before April 2005, LAS was performed only for early colorectal cancer. Subsequently, the indications for LAS were expanded to include advanced colorectal cancer. Patients who had a diagnosis of T4 tumor or Stage IV were excluded from the indication for LAS, and the operative technique was decided upon by the each of the surgeons who took the preoperative state of the patients or the hopes of the patients into account.

The medical records of the participating patients were reviewed retrospectively and age, sex, type of operation, tumor location, and complication, were recorded. The physiologic score (PS) of POSSUM was used for preoperative physiologic evaluation. PS represented the

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TABLE 1. Preoperative Patients Characteristics

	OS Group (n = 78)	LAS Group (n = 51)	P
Age (y)	76 (71-93)	75.5 (71-89)	NS
Sex (M/F)	43/35	32/19	0.02
Tumor Location			
Colon	67	43	NS
Rectum	11	8	
ASA Score			NS
1 or 2	63	37	
3 or 4	15	4	
Performance Status			NS
0 or 1	70	49	
2≥	8	2	
PS in POSSUM	23 (13-39)	22 (16-35)	NS
PNI	42.6 (21.9-57.1)	46.9 (36.0-60.0)	< 0.0001

LAS indicates laparoscopically assisted surgery; NS indicates nonsignificant; PNI, Prognostic Nutritional Index; POSSUM, Physiological and Operative Severity Score for Enumeration of Mortality and Morbidity; PS, Physiologic Score; OS, open surgery.

sum score of 12 factors, including age, heart, and lung functions. The Operative Severity Score (OSS) in POSSUM was calculated, using 6 factors related to operative severity, procedures, blood loss, peritoneal soiling, presence of malignancy, and mode of surgery.[15] The PNI was used to determine the preoperative nutritional state and represented the levels of serum albumin and total lymphocyte count of peripheral blood, as described earlier.[16] Postoperative complications were classified according to NCI-CTC AE version 3.0 by colorectal surgeons (*webapps.ctep.nci.nih.gov/webobjs/ctc/webhelp/welcome_to_ctcae.htm*). Operative mortality was defined as death on the same admission or within 30 days of surgery. Data of patients, whose operative procedure was switched from laparoscopy to OS, were analyzed as the LAS group by intent-to-treat analysis. All patients were followed at least for 3 months and remained under observation after surgery. Postoperative morbidity and mortality of LAS group and OS group were analyzed retrospectively.

Statistical Methods

Results are expressed as median values. Differences in age, PS, PNI, and operative factors between the groups were analyzed by the Mann-Whitney *U* test. Other factors were analyzed by Fischer's exact probability test. Statistical significance was established at $P < 0.05$.

RESULTS

A total of 129 patients were analyzed, including 73 men and 56 women. There were 78 laparoscopically assisted and 51 open procedures. Table 1 lists the preoperative factors for both groups. The PS values were similar for the two groups (OS: 23 points, LAS: 22 points). PNI was significantly higher in the LAS group (46.9 points) than in the OS group (42.6 points). However, there was no significant difference between the OS group and the LAS group in terms of the American Society of Anesthesiology score, tumor location, and performance status.

Table 2 depicts the postoperative complications of the 2 groups. One perioperative death was recorded in the LAS group, but no laparoscopy-related morbidity was observed. This patient died of postoperative pneumonia because of long steroid use for rheumatoid arthritis. The complication rate for the entire group was 40.3%, which was similar to the predicted morbidity rate in POSSUM of 50.4% ± 24.2%. The complication rate for the OS group was 51.3%. This was significantly higher than the 23.5% in the LAS group, which was within the prediction range of POSSUM ($P = 0.001$).

The most common operative procedures were right colectomy and sigmoidectomy with no differences between the 2 groups. The operative factors are shown in Table 3. The mean operating time was significantly longer, and mean blood loss was significantly smaller in the LAS than in the OS group. The conversion rate was 5.9% (3 of 51 patients) in the LAS group. The reasons for conversion were poor general condition in 1 patient and adhesions in 2 patients. None of the conversions was due to technical problems. Although LAS was performed only for early colorectal cancer before April 2005, and subsequently, the indications for LAS were expanded to include advanced colorectal cancer, we found no significant difference between the earlier and the latter periods in preoperative factors, including PS and PNI (data not shown).

We also examined PS, OSS, and PNI in the OS and LAS groups in terms of complications. There were significant differences in PS, OSS, and PNI between patients of the OS group with and without complications (Fig. 1). In the LAS group, only OSS was significantly lower in those without complications than in those with complications, but there were no differences in PS and PNI in the LAS group (Fig. 2).

Then, we carried out the univariate analysis of preoperative and postoperative factors for postoperative complications (Table 4). There was significant difference between those with and those without complications in

TABLE 2. Postoperative Complications

	Total Patients (n = 129)	OS Group (n = 78)	LAS Group (n = 51)	P
Anastomotic hemorrhage	4 (3.1)	2 (2.6)	2 (3.9)	0.93
Anastomotic leakage	4 (3.1)	2 (2.6)	2 (3.9)	0.93
Wound infection	29 (22.5)	25 (32.1)	4 (7.8)	< 0.001
Cardiac or pulmonary disease	4 (3.1)	4 (5.1)	0	—
Delirium	14 (10.9)	10 (12.8)	4 (7.8)	0.28
Bowel obstruction	9 (7.0)	8 (10.3)	1 (2.0)	0.07
Other infection (urinary, catheter etc.)	7 (5.2)	6 (7.7)	1 (2.0)	0.16
Death	1 (0.8)	0	1 (2.0)	—
Total complication rate	52 (40.3)	40 (51.3)	12 (23.5)	0.001

LAS indicates laparoscopically assisted surgery; OS, open surgery.

TABLE 3. Comparison of Operative Factors

	OS Group (n = 78)	LAS Group (n = 51)	P
Conversion		3 (5.9)	
Operative time (min)	170 (78-760)	216 (110-505)	0.0008
Blood loss (mL)	280 (40-12890)	50 (5-1500)	< 0.0001
Stages I, II/III, IV	23/55	32/19	0.0002
OSS in POSSUM	12 (9-30)	11 (8-21)	< 0.0001

LAS indicates laparoscopically assisted surgery; OS, open surgery.

terms of PS, OSS, PNI, operative procedure, and blood loss ($P < 0.05$). On multiple logistic regression analysis, OSS was an independent risk factor for postoperative complication ($P = 0.026$), suggesting that less invasive surgery is associated with lower postoperative complications (Table 5).

DISCUSSION

Laparoscopic surgery has generally been recognized as minimally invasive. Especially for elderly patients, its impact on postoperative complication and recovery has been documented. Stewart et al[14] reported that the complication rates were 33.3% and 16.7% for OS and laparoscopic surgery, respectively, in a cohort study of patients older than 80 years. Delgado et al[12] presented data from a prospective colon cancer trial of patients aged more than 70 years, which demonstrated a higher postoperative complication rate in OS than in laparoscopic surgery. Their complication rates were 31.3% in OS and 10.1% in laparoscopic surgery. Stocchi et al[13] reported in a matched-control study a lower incidence of postoperative complication in patients aged more than 75 years who were operated upon laparoscopically (14.3%) compared with those who underwent OS (33.3%). Sklow et al[8] used the classification of complications defined by Clavien et al.[17] However, as most reports included retrospective analysis, and definition of elderly, assessment of preoperative patient status, criteria of complications, and indication for laparoscopic surgery varied from one study to another, no firm conclusion could be drawn.

In this study, we evaluated the impact of laparoscopic surgery on elderly patients, using POSSUM and PNI as objective indexes. The incidence of all complications in the entire group was 40.3% with 50% in the OS group and 23% in the LAS group. The incidence rate in this study was higher compared with other reports,[9,12–14,18] and some reports showed that the surgical outcomes of LAS were better than those predicted by POSSUM,[10,11] probably because all complications were recorded in our study according to the NCI-CTC AE version 3.0 (*webapps.ctep.nci.nih.gov/webobjs/ctc/webhelp/welcome_to_ctcae.htm*). Even minor complications that might have little or no influence on postoperative hospital stay or mortality were counted. Nevertheless, we understand that the incident rate is within acceptable range.

We also compared POSSUM and PNI scores of our cohort with those of other reports to evaluate the feasibility of using these preoperative indexes.[15,19–21] POSSUM has been used clinically to predict postoperative morbidity and mortality since its introduction in 1991.[15] Our data were compatible with other reports and within the prediction range, suggesting that it is feasible to use the POSSUM score for the prediction of postoperative complications. In contrast, the American Society of Anesthesiology scores and performance status were also analyzed but no difference was detected, suggesting that these variables are not useful for predicting differences in postoperative complications between the laparoscopic and open procedures. With regard to the PNI, which was reported by Buzby et al[22] and is based on serum albumin level, serum transferin level, thickness of triceps skinfold, and skin test reaction, these variables are impossible to measure retrospectively. Therefore, we used the simplified PNI score reported by Onodera et al,[16] which is based on serum albumin and total lymphocyte count. The result showed a significant difference in preoperative PNI scores in terms of postoperative complications, suggesting that the PNI score might be useful in the prediction of postoperative complications, but might be the reflection of the selection bias in our study.

In our study, PS in POSSUM was not different between laparoscopic and OS groups, suggesting that the patient selection bias for the laparoscopic surgery was negligible, because we had actively treated patients laparoscopically. In the OS group, we found significant differences

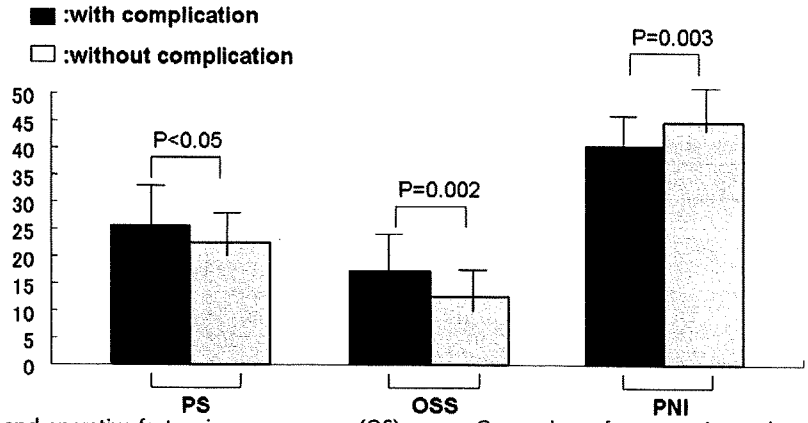

FIGURE 1. Preoperative and operative factors in open surgery (OS) group. Comparison of preoperative and operative factors between patients with and without complications of the OS group. Data are shown as median values. OSS indicates Operative Severity Score; PNI, Prognostic Nutritional Index; PS, Physiologic Score.

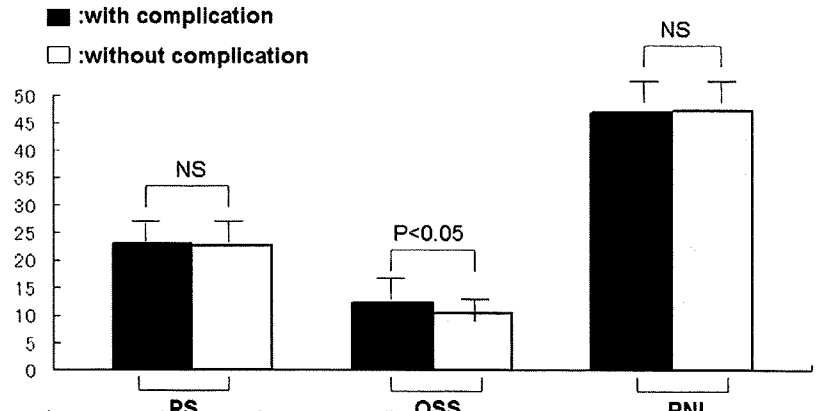

FIGURE 2. Preoperative and operative factors in laparoscopically assisted surgery (LAS) group. Comparison of preoperative and operative factors between patients with and without complications of the LAS group. Data are shown as median values. OSS indicates Operative Severity Score; PNI, Prognostic Nutritional Index; PS, Physiologic Score.

in PS between patients with and without complications. This finding suggests that the preoperative patient status seems to influence the postoperative course under more invasive conditions. On the other hand, in the less invasive laparoscopic surgery, preoperative patient status was not associated with postoperative complications, suggesting that laparoscopic surgery is not contraindicated for patients with worse preoperative conditions.

In our study, PS and PNI had a significant difference between those with and without complications on univariate analysis in preoperative factors, and OSS and blood loss had a significant difference in operative factors ($P\& < 0.05$). On multiple logistic regression analysis, OSS was only an independent factor for postoperative complication ($P = 0.026$), and PS and PNI were not. This result suggested that less invasive surgery was associated with reducing postoperative complications. LAS was generally considered to be a less invasive surgery than OS,[8,12–14,18] and our study provided similar results. Therefore, it was suggested that LAS was associated with a lower incidence of complications compared with OS in elderly patients with colorectal cancer. However, LAS was performed only for early colorectal cancer before April 2005, and the indication of LAS was expanded for advanced colorectal cancer in the latter period at our department. This bias may be associated with our results that postoperative complications were less in the LAS group than in the OS group.

The PNI was significantly higher in patients who underwent laparoscopic surgery, suggesting that laparoscopic surgery was performed in patients with a better nutritional condition. Furthermore, in the OS group, there was a significant difference in PNI between those with complications and those without. It was suggested that PNI was associated with postoperative complications under the invasive condition, if the LAS group is compared with the OS group or, comparing the complications group with the no complications group. Considered together, these results highlight the importance of the nutritional state on postoperative complications. A relationship between nutritional state and morbidity was proposed earlier,[23] but there are only a few reports suggesting a correlation between nutritional status and postoperative complications.

Although PS was not different between the OS and the LAS groups, preoperative nutritional status may influence the rate of postoperative complications between the two groups. A prospective study must be carried out, comparing open and laparoscopic surgery in similar patient background.

We examined the feasibility and maturity of laparoscopic surgery. In this study, all colorectal cancers were included. Three patients were converted, and the incidence of complications was 23%. On the other hand, no complications, peculiar to laparoscopic surgery, were encountered in this cohort. These results were not inferior

TABLE 4. Univariate Analysis of Preoperative and Operative Factors for Postoperative Complications

	With Complication (n = 52)	Without Complication (n = 77)	*P*
Age	76 (71-93)	76 (71-89)	NS
Sex (M/F)	29/23	46/31	NS
PS	24 (13-36)	21 (16-39)	0.049
OSS	13 (9-30)	11 (8-24)	< 0.001
PNI	42.7 (21.9-60.0)	46.5 (28.9-57.1)	0.003
BMI	21.3 (13.3-38.1)	22.7 (15.2-28.4)	NS
OS/LAS	12/40	39/38	0.005
Blood loss	275 (10-12930)	120 (0-1640)	< 0.001
Operative time	200 (82-760)	200 (78-2115)	NS
ASA 1 or 2 /3 or 4	42/10	68/9	NS
Performance status 0 or 1/ 2 or 3 or 4	46/4	73/4	NS

NS indicates nonsignificant.

TABLE 5. Multivariate Analysis of Preoperative and Operative Factors for Postoperative Complications

	Odds Ratio	95% CI	*P*
PS	0.969	0.889-1.056	0.469
OSS	0.852	0.741-0.981	0.026
PNI	1.058	0.889-1.056	0.157
Blood loss	0.999	0.998-1.001	0.476

CI indicates confidence interval; PNI, Prognostic Nutritional Index; PS, Physiologic Score; OSS, Operative Severity Score.

to those reported in earlier studies that examined the feasibility of laparoscopic surgery for elderly patients with colorectal cancer.[7,8,10–14,18,24]

A number of reports have evaluated the usefulness of laparoscopic surgery in elderly patients;[7,10–14,18,24] however, the majority of such studies are retrospective in nature, including this study. In this context, Frasson et al[25] found fewer infectious complications in elderly patients who underwent laparoscopic surgery than in OS in a randomized control study. A randomized prospective study that includes only elderly patients is required to compare laparoscopic and OS under similar preoperative patient conditions.

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結腸癌
——治療の実際——

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結腸癌
治療の実際

Diagnosis and therapy for colon cancer

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key words：結腸癌，手術，大腸癌ガイドライン，大腸癌取扱い規約

はじめに

近年のわが国における大腸癌の増加は顕著であり，今後も増加の一途をたどることが確実視されている[1]。一方，1980年代以降，大腸癌に関する研究はさまざまな発展をとげ，飛躍的な治療効果の改善をもたらした。とくに臨床の現場では，内視鏡的診断・治療の進歩，抗癌剤治療の発達，腹腔鏡手術の登場などが大きな役割を果たしている。

わが国では，大腸癌治療の均てん化を図るために『大腸癌取扱い規約第7版』に沿った『大腸癌ガイドライン医師用2005年度版』が作成された。本ガイドラインにより，「標準的治療方針の提示」，「施設間格差の解消」，「過剰診療・治療，過小診療・治療の解消」などが達成されつつある[2][3]。大腸癌治療は，手術以外の治療法の重要度も増し，近年では手術治療を中心に内視鏡的治療や化学療法などを駆使した集学的治療が行われるようになってきた。本稿では集学的治療のなかでの外科治療という観点から，結腸癌外科治療について述べる。

術前検査

結腸癌の治療法を決定するためには占居部位・深達度・リンパ節転移の程度・遠隔転移などの評価が必要である。また併存病変や大腸癌イレウスの程度などによっても治療方針や術式が変わってくるので可能な限り正確で詳細な術前情報を得ることが必要である。

1. 問　診

問診では家族歴や既往歴が重要である。全大腸癌の約1～5％にHNPCC（hereditary nonpolyposis colorectal cancer；遺伝性非ポリポーシス大腸癌）が存在することが知られている。問診によりAmsterdam Criteria ⅡやJapanese clinical criteria（表1）を満たした場合にHNPCCと診断される。HNPCC症例では，結腸全摘や大腸全摘が考慮される場合もある。またHNPCC関連癌の存在も知られており，サーベイランスでは他臓器癌の検索も行う必要がある。常染色体優性遺伝であり家族を含めたサーベイランスを行い治療に役立てることも重要である[4]。

2. 直腸診

腫瘍と肛門との距離，腫瘍サイズ，可動性などを診断するために非常に有用で簡便な検査である。直腸癌に限らず必須であり，結腸癌に合併する直腸肛門病変や腹膜播種の診断にも有効な場合がある。

3. 腫瘍マーカー（CEA）

大腸癌全体の約40％で高値となる。とくに遠隔転移を有するStage Ⅳ症例では80％で高値であり，また，再発症例では約70％で上昇する。CEAの上昇は遠隔転移を示唆するとともに再発例の早期発見に非常に有用とされる[5]。

4. 下部消化管内視鏡検査

生検による確定診断だけでなく，肉眼型・表面構造から壁深達度を推測するのに非常に有用である。表面型大腸癌では色素散布や拡大内視鏡，さらに最近ではNBI内視鏡（narrow band imaging；狭帯域光観察）を使用して肉眼型やpit pattern（図1，2）から腫瘍の深達度診断を行い，内視鏡的治療の適応を決定す

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表1　HNPCC 診断基準

Revised ICG-HNPCC Criteria（Amsterdam Criteria Ⅱ）1998

家系内にすくなくとも3名以上のHNPCCに関連した腫瘍（大腸・子宮体部・小腸・尿管・腎盂）※

1）そのうち1名はほかの2名に対して第一度近親者（親・子・兄弟）であること

2）すくなくとも2世代にわたって発症していること

3）すくなくとも1名は50歳未満で診断されていること

4）家族性大腸腺腫症（FAP）が除外されていること

5）腫瘍の組織学的診断が確認されていること

※大腸癌研究会による改訂 Amsterdam Criteria Ⅱでは，HNPCC関連腫瘍に胃癌を加え5）を除外する

Japanese clinical criteria（1992大腸癌研究会）

A：第一度近親者に発端者を含め3例以上の大腸癌患者を認める

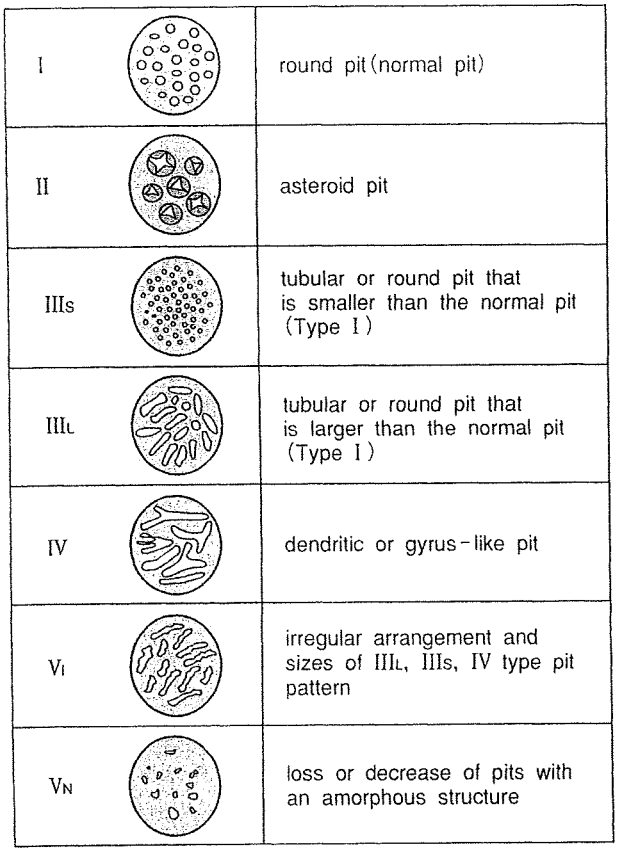
B：第一度近親者に発端者を含め2例以上の大腸癌患者を認め，なおかつ下記いずれかの条件を満たす大腸癌

a）50歳以下の若年大腸癌

b）右側結腸癌

c）同時性あるいは異時性多発大腸癌

〔文献4）より引用〕



〔文献6）より引用〕

図1　大腸腫瘍の pit pattern 分類

pit pattern	adenoma		cancer		total
	mild - mod	SEV	M	SM	
IIIL	10877	2268	655	0	13800
IV	1916	797	735	119	3567
IIIs	189	63	36	10	298
V I	92	133	342	231	798
V N	0	14	66	263	343
total	13074	3275	1834	623	18806

〔文献7）より引用〕

図2　pit pattern 診断と病理組織との対応

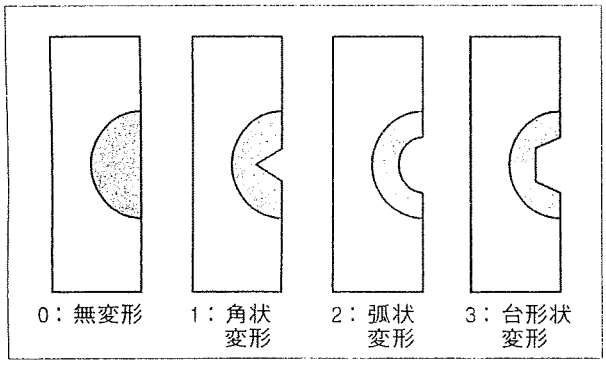
る[6,7]。

5. 超音波内視鏡検査

とくに表面型大腸癌の壁深達度の診断に優れている。進行癌の場合，他臓器浸潤の有無や腸管旁リンパ節転移の有無に有用な場合もある[8,9]。

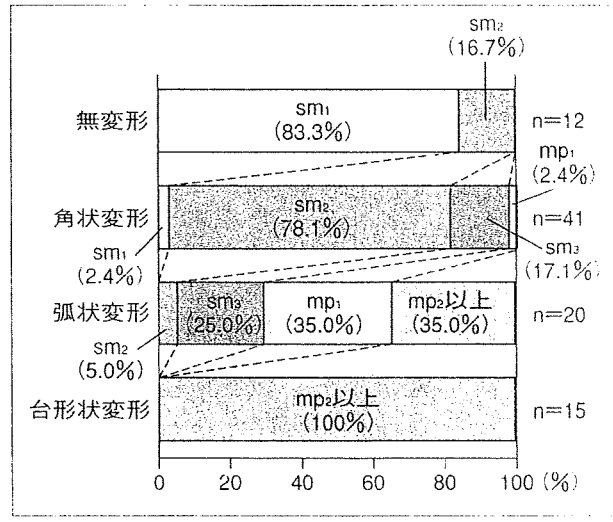
6. CT/MRI/PET-CT

CTは進行癌の原発巣の広がりや遠隔転移巣の有無の診断に有用である。MRIは腫瘍の消化管壁外への進展や隣接臓器・骨盤壁への浸潤の有無を診断するのに有用である。なかでもEOBプリモビスト造影MRIは肝転移巣の描出に非常に有用である。肝細胞特異性常磁性造影剤，EOB・プリモビスト（Gd-EOB-DTPA；ガドキセト酸ナトリウム）が肝細胞に取り込まれるため，肝細胞分布相における病変-肝臓コントラストにより病変が検出される。とくに肝細胞造影相における1cm未満の微小転移の検出能ではCTに対する優位性が示されている[10]。PET-CTは最近急速に普及してきた検査法である。本検査は腫瘍の糖代謝の多寡を画像化する診断法でさまざまな臓器や腫瘍を検出できる特徴を有している。大腸癌ではFDG（fluoro-deoxy-glucose）が原発巣だけでなく，転移巣にも良好に集積する。1回で全身の撮影が可能なPET-CTは，遠隔転移の検出にもっとも威力を発揮する。肺転移や肝転移，リンパ節転移に対しても有用



〔文献13)より引用〕

図３　大腸癌における側面変形の型分類



〔文献13)より引用〕

図４　大腸癌における側面変形と深達度

であるが，CT/MRI などの形態診断だけでは鑑別困難な局所再発や腹膜再発の診断に有用性が高い[11,12]。同時性重複癌・多発癌の検出にも有効で，大腸癌では見落とし病変の検出や内視鏡通過不可能な狭窄病変の口側腸管のスクリーニングに有効である。

7.　注腸検査

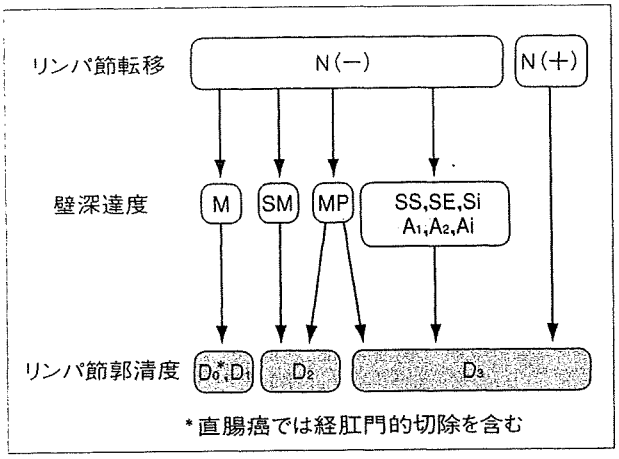
結腸癌症例に必須ではないが，大腸の全体像の把握や病変の客観的位置同定などに有用な検査法である。側面変形像から腫瘍深達度（側面像の型分類；**図3，4**）[13]を診断するのに有用である。

術前腸管処置

ポリエチレングリコールなどを使用して腸管内容物を洗い流す機械的腸管処置と経口抗菌薬を用いて，腸内細菌量を減らす化学的腸管処置に分けられる。最近，機械的腸管処置の施行が縫合不全をむしろ増加させるとの報告があった[14]が，未だ十分なエビデンスとはいえず，術中操作も容易となるため，機械的腸管処置を行うのが一般的である。化学的前処置は，腸内細菌量を減らし，手術部位感染を減らす目的があるが，むしろこれが増加するとの報告[15]もあり，最近では行わない施設も増えている。

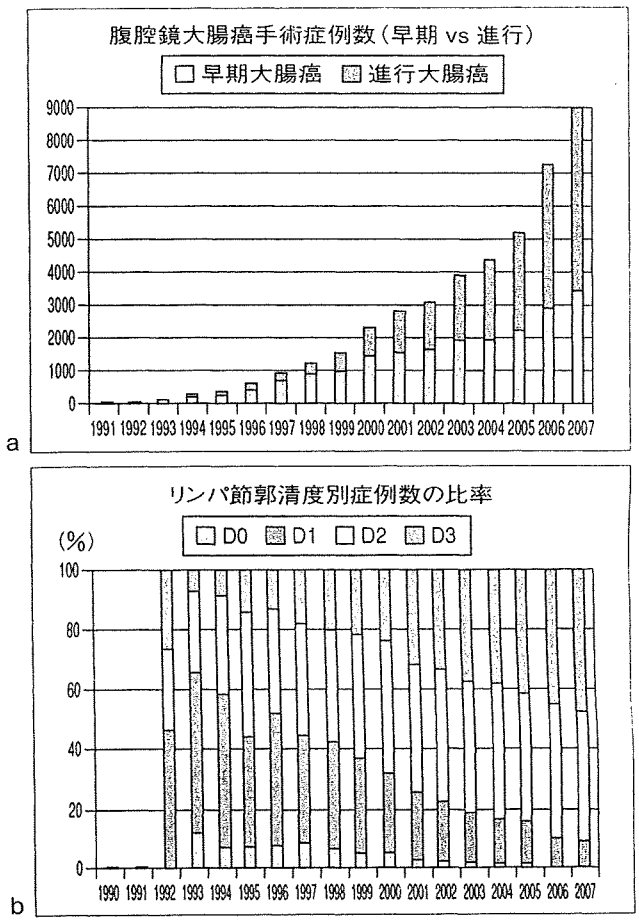
根治手術

『大腸癌治療ガイドライン』で示されている手術の絶対適応は下部消化管内視鏡検査で進行癌あるいは明らかな sm 深部浸潤癌と診断された症例，また内視鏡的治療で total biopsy の結果，垂直断端陽性と診断された症例である。加えて，内視鏡的摘除病変の深達度が sm 癌で，かつ①浸潤距離が1000 μm 以上，②リンパ管侵襲（ly 因子）もしくは静脈侵襲（v 因子）である脈管侵襲陽性，③未分化腺癌・低分化腺癌，のいずれかを認めた場合にも外科的切除を考慮する。手術術式に関しては腫瘍の深達度とリンパ節転移の有無に応じて D2リンパ節郭清（以下 D2郭清）もしくは D3リンパ節郭清（以下 D3郭清）が推奨される。術前検査でリンパ節転移陽性と診断されている症例では D3郭清が必要で，リンパ節転移陰性と診断された症例でも固有筋層を越える深達度を有する SS または A 以上の症例でも D3郭清が必要である。固有筋層にとどまる MP 症例では D2郭清で十分であるがリンパ節転移陽性症例が少なからず存在することから D3郭清を行ってもよいとされている。SM 症例では約10%のリンパ節転移率があるため，D2郭清以上が推奨される（図5：『大腸癌治療ガイドライン』のアルゴリズム）。このようにして決定される郭清範囲を開腹で行うか，腹腔鏡手術で行うかには施設間格差がある。内視鏡外科学会のアンケート調査によると，わが国の多くの先進的施設では D3郭清が腹腔鏡手術で行われるようになった[16]（**図6**）。しかし『大腸癌治療ガイドライン』では「大腸癌に対する標準術式としての腹腔鏡手術はあくまで外科手術療法の一つという位置づけであり結腸癌・直腸 S 状結腸部癌の Stage 0もしくは Stage Ⅰの症例に適応とされる治療」と示されている。海外ではすでに進行大腸癌に対する腹腔鏡手術の根治性に関する RCT（ランダム化比較試験）が報告されており，単施設から世界で初めて報告された Barcelona study や多施設で行われた COST study，CLASICC study などでは，根治性に関して腹腔鏡手術は開腹手術とおおむね同等という結果であった。わが国では2004年に開始された JCOG0404 study「進行大腸癌に対する



〔文献3)より引用〕

図5　Stage 0～Ⅲ大腸癌の手術治療方針



〔文献16)より引用〕

図6　わが国の大腸癌治療

腹腔鏡手術と開腹手術の根治性に関するランダム化比較試験」が現在進行中であり，今後の結腸癌に対する腹腔鏡手術の適応拡大はこの結果を待ってなされるべきと考える。

1. 体　位

開腹手術：仰臥位

腹腔鏡手術：低位砕石

2. 開腹創

開腹手術では，約10cmの腹部正中切開をおく。切除範囲に合わせて創を上下へ移動させる。

腹腔鏡手術では合計5ポートで行う。腸管授動が完了したらもっとも腸管の取りだしやすい位置に約5cmの小切開をおき，腸管の切除吻合を行う（**図7**）。

われわれは手術創の開創と保護・感染予防のため，Alexis™ wound protectorを使用している。開腹手術では小腸はガーゼに包みできるだけ腹腔内に納めて視野確保につとめている。

3. 腸管の剝離授動

盲腸・上行結腸・下行結腸・S状結腸・直腸S状結腸部癌での腸管の剝離授動方法には外側アプローチと内側アプローチ（**図8**）があげられる。文字通り，外側アプローチは，腸管外側の剝離授動である。開腹のイメージに近いため，腹腔鏡手術が導入された当初は多くの施設でこのアプローチ法が行われていた。その後導入された内側アプローチは主幹血管近傍から腸間膜の剝離授動を行う方法であり，主幹血管処理を先に行うことから後述するnon-touch isolation techniqueの観点からも理にかなったアプローチ方法とされた。内側アプローチは開腹手術ではなじみのない術野の手技であることから修得に時間を要すると考えられていたが，手技に関するビデオ教材が多く手に入る現状では必ずしも難しいアプローチ方法とはいえない。どちらの方法もいかにして安全に早く後腹膜下筋膜を同定するかが重要である。内側アプローチは腹腔鏡手術が広まるにつれ見直された術式であり，われわれは腹腔鏡手術の技術を開腹手術にフィードバックさせる意味でも時に開腹手術で内側アプローチを行うことがある。開腹手術でも腹腔鏡手術でもそれぞれのアプローチ方法を腫瘍の占居部位や癒着の程度，術者の慣れなどに応じて選択されるべきである。横行結腸癌に関しては先に述べた進行大腸癌に関するさまざまなRCTでも適応症例とされていない。横行結腸進行癌の血流支配はバリエーションが多く，郭清を腹腔鏡手術のみで行うことは非常に難易度が高いので，横行結腸癌に対する腹腔鏡手術は標準手術ではないと考えられている。われわれは横行結腸癌症例ではリンパ節郭清のみを直視下に行い，腸管の剝離・授動にはHALS（hand assisted laparoscopic surgery）を行う場合もある。また腫瘍径が5cmを超えるような症例でも腫

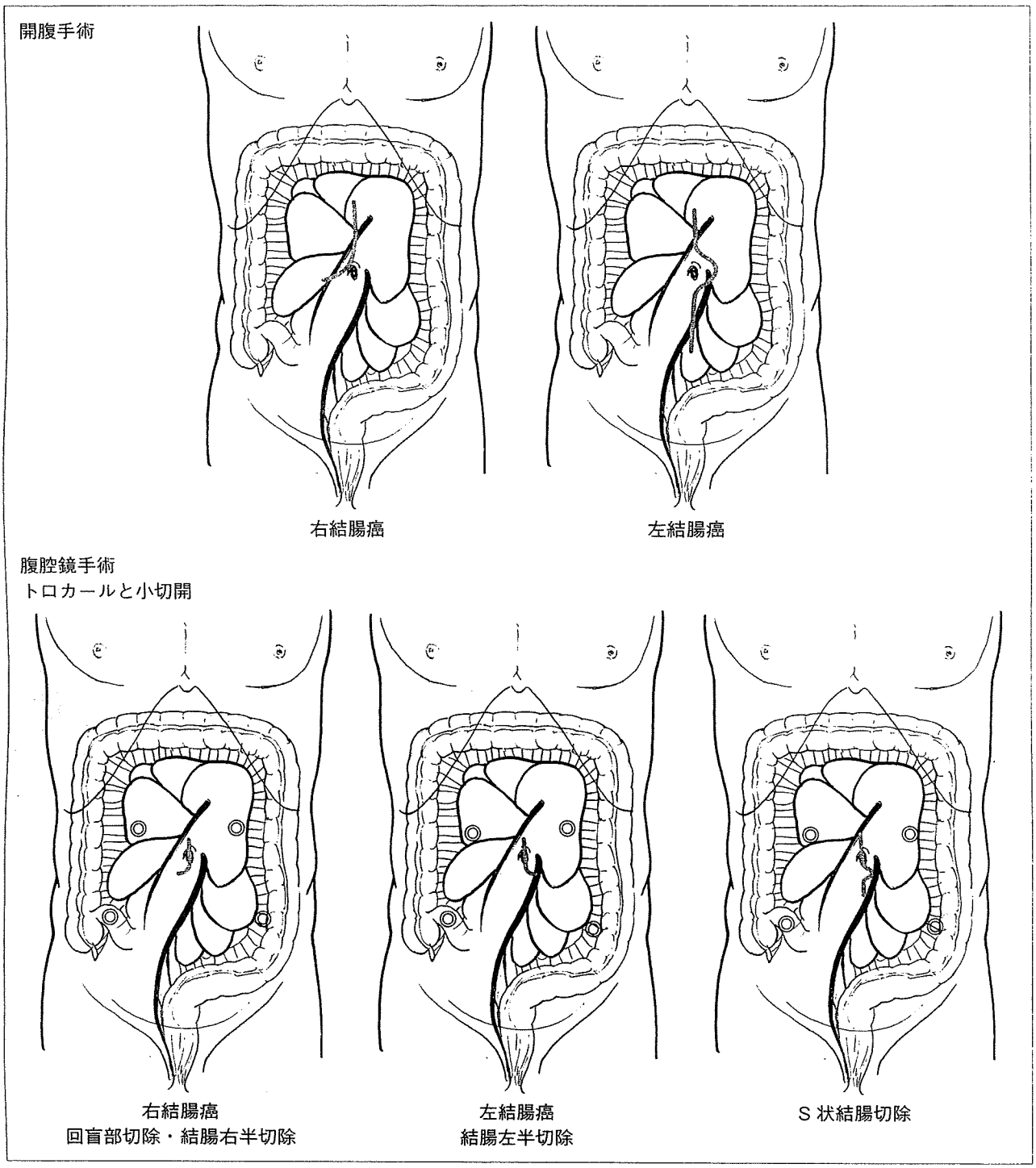


図7　手術創

瘍を取りだす小切開が7cm以上となるためHALSを考慮している[17]。

4. Turnbullの non-touch isolation technique

本来は，早期に血流遮断を行うことで遠隔転移を予防する方法として提唱されたが，エビデンスはない。しかし，できるだけ腫瘍に直接触れることなくen blocに病巣を切除するという考えは腫瘍外科医に不可欠な姿勢である[18]。

5. 腸管切除範囲の決定

結腸の切除範囲は支配動脈と腫瘍との位置関係から4つに類型され（**図9**）決定される。①支配血管が腫瘍直下にある場合，②支配動脈が腫瘍辺縁より10cm以内に1本ある場合，③支配動脈が腫瘍辺縁から10cm以内に2本ある場合，④支配動脈が腫瘍辺縁から10cm以上離れて2本ある場合である。それぞれ図9に示すように腸管の切除範囲が推奨されている。

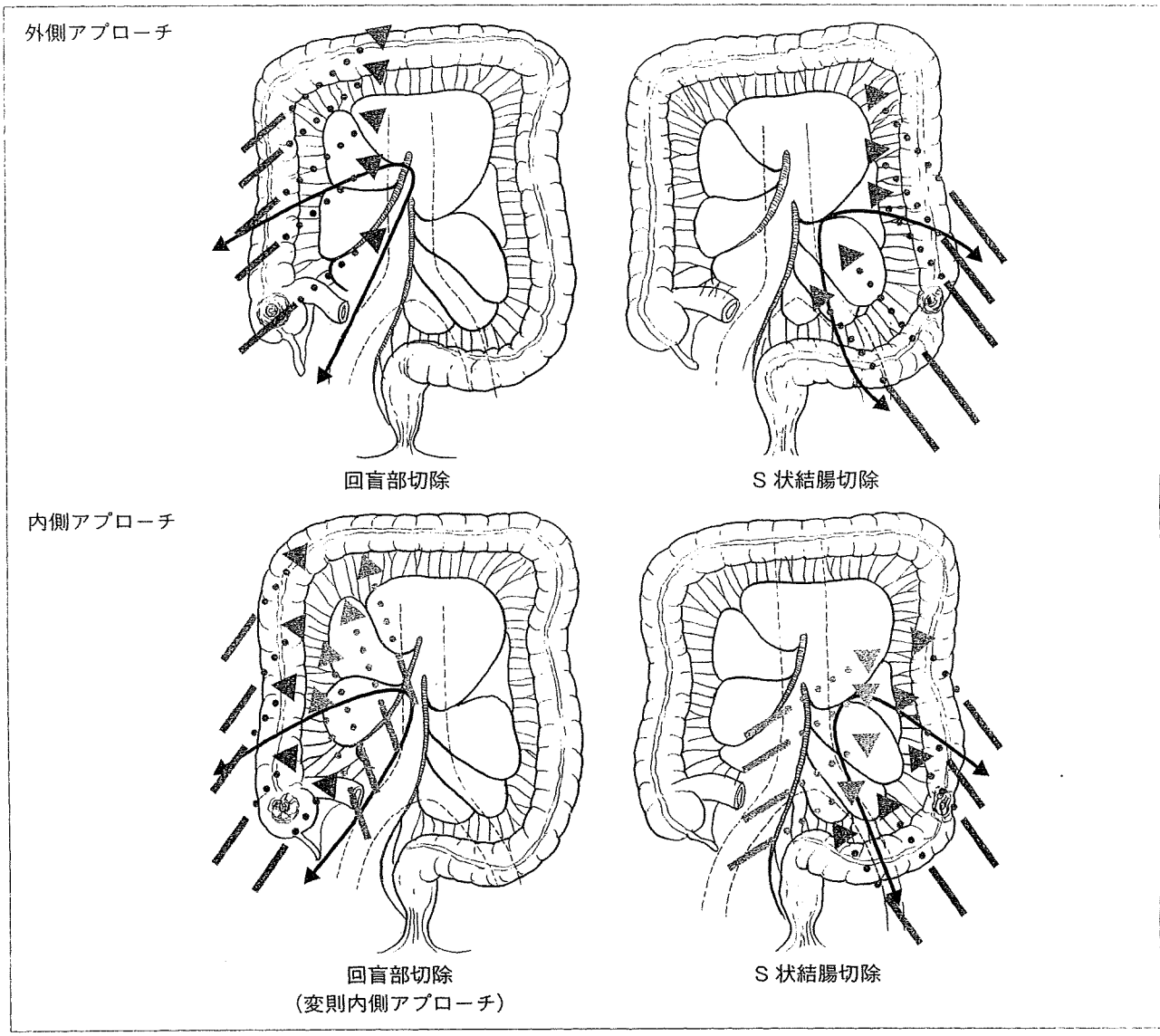


図 8　アプローチ

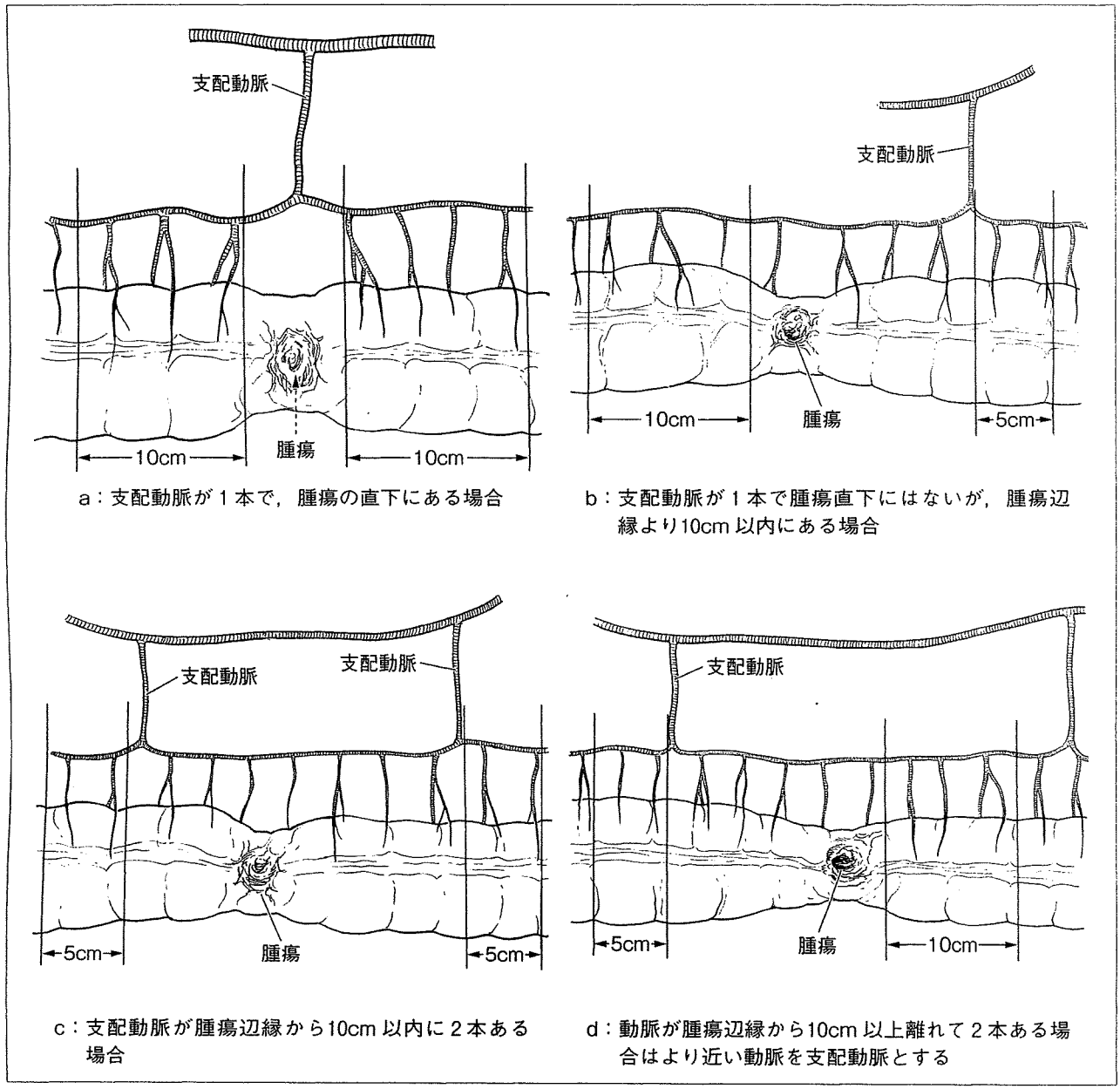
再建方法

1.　手縫い法

吻合の基本原則は，血流障害の防止，感染の防止，吻合部への緊張の排除である。腸間膜の処理を腸管の長軸方向に直交するように行い，虚血範囲を作らないように工夫する。また縫い代用の結腸壁の露出は血流障害を防止する目的で約 1 cm 以内としている。感染予防には，腸管内容物をガーゼで拭き取ってから吻合を開始する。吻合部に緊張がかからないように腸管の授動を十分に行う必要がある。手縫いによる腸管吻合法は一層縫合と二層縫合に大別される。前者の代表的な縫合法には Gambee 縫合があげられ，後者の代表的な縫合法には Albert-Lembert 縫合（全層縫合＋漿膜筋層縫合）と層々吻合（粘膜縫合＋漿膜筋層縫合）の 2 種類があげられる（図10）。層々吻合は，各層を正しく接合させるものであり，血流の豊富な粘膜下組織を確実に接合させることが腸管の創傷治癒に重要であるという知見をもとに理にかなっているとされてきた。しかし近年行われるようになった器械吻合は全層の吻合であるが，臨床的な問題は生じていない。もっとも古典的な Albert-Lembert 縫合の漿膜筋層縫合は，全層縫合の縫い目から内容の漏出を避けるためと，吻合部への張力に対する補強の意味を有すると理解されている。一方，層々吻合では漿膜筋層縫合が吻合の張力を支える主体であり，Albert-Lembert 縫合より密に縫合することが必要である。

2.　functional endo-to-endo anastomosis（機能的側々吻合；図11）

近年，腹腔鏡手術の発展に伴い急速に普及している吻合法である。縫い代用の腸間膜処理が不要なこと，



〔文献2)より引用〕

図9　腸管切離ライン

腸管の口径差が問題にならないことが利点である。自動縫合器で切離した口側・肛門側の腸管を平行に並べて切離端の腸間膜対側を小さめに切開し，線状吻合器を挿入し，腸間膜対側で側々吻合する。線状吻合器を抜去し，出血がないことを確認して，両方の切開部分をAllis鉗子で把持して線状吻合器で閉鎖する。最後に線状吻合器で側々吻合した先端と切開部位を線状吻合器で閉鎖したstaple lineの交叉部は，漿膜筋層縫合を2～3針行い補強する。

術後補助化学療法

欧米では，1990年代に結腸癌に対する5-FU+LV併用の補助化学療法が確立された[19]。『大腸癌治療ガイドライン』では，肉眼的に治癒切除（根治度A）が行われた結腸癌Stage Ⅲに対して術後補助化学療法として5-FU+LV併用の代表的なレジメであるRPMI（Roswell Park Memorial Institute）レジメが推奨されている。また，Stage Ⅱのうちハイリスク症例に対する術後補助化学療法のエビデンスはないが，術後補助化学療法を行う場合もあると記載されている。最近では経口5-FU系抗癌剤であるUFT+LV療法やcapecitabine療法が5-FU+LVと同等であることが証明され[20]，内服抗癌剤治療が，徐々に治療法として認識されるようになっている。

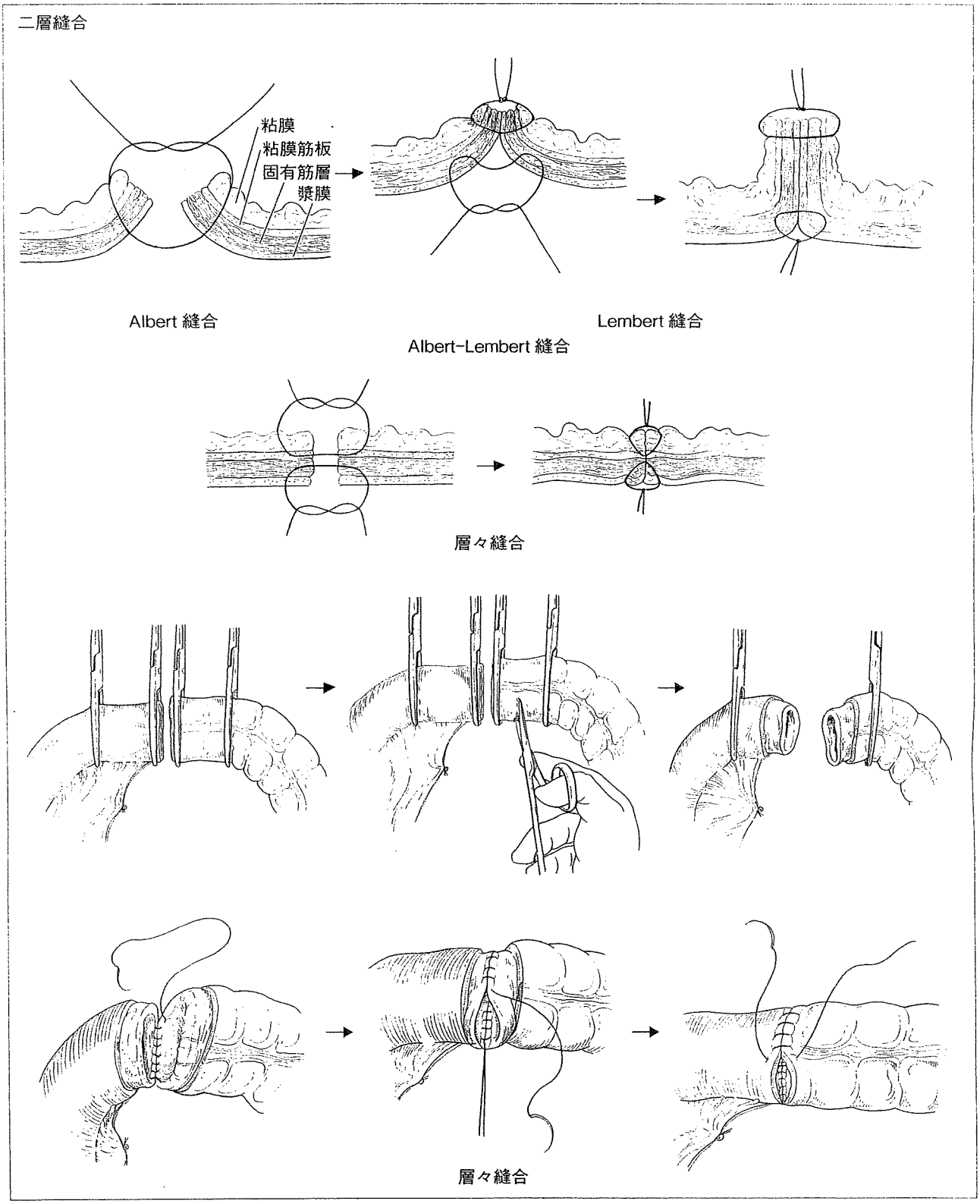


図10　吻合法（手縫い）

遠隔転移に対する外科治療

『大腸癌治療ガイドライン』によると結腸癌の約11.4％に肝転移を，1.6％に肺転移を，6.4％に腹膜転移を有するとされる。肝や肺に遠隔転移を有する症例では，転移巣の切除が可能であれば原発巣切除をしたうえで転移巣切除を考慮する。また腹膜転移に関しても，P1では原発巣を含めた完全切除が望ましく，P2では切除可能な場合に原発巣を含めた完全切除を考慮するとされている。大腸癌の場合，このように遠

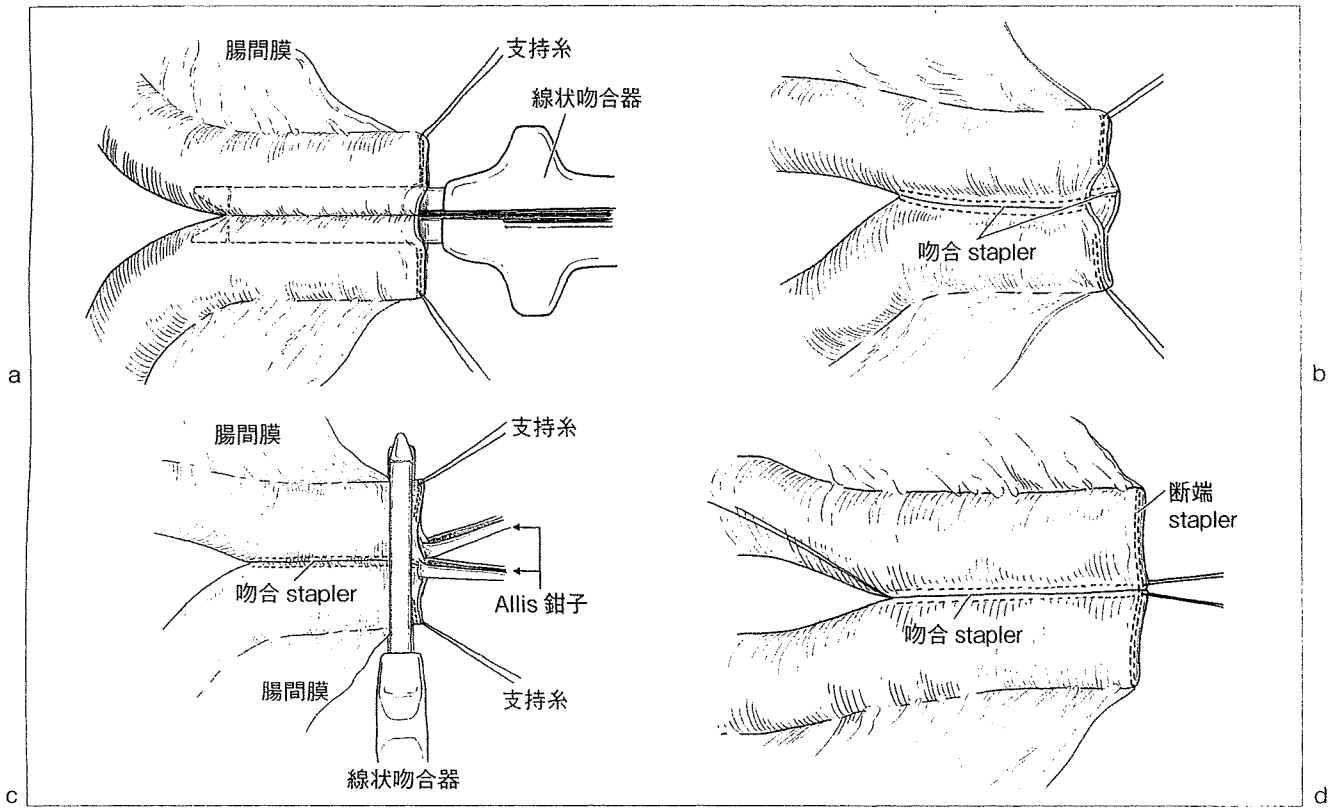


図11　吻合法（器械）

隔転移を有する症例でも外科的切除をすることで少なからず治癒が望める症例が存在することが知られているため，切除による治療をまず考慮する。

集学的治療

近年の新規抗癌剤・分子標的治療薬の登場により，高度進行大腸癌や切除不能大腸癌に対する治療成績の向上が報告されている。前項で述べた肝転移・肺転移・腹膜転移に対する外科的切除による治療と抗癌剤治療を組み合わせた集学的治療が行われるようになった。切除後の再発予防に化学療法を使用したり，切除不能例に対して化学療法治療を先行し可能であれば遠隔転移巣を切除するといった治療法である[21]。また放射線療法は直腸癌に対する骨盤内再発予防やダウンステージを目的とした補助療法として確立されているが，結腸癌では骨転移や脳転移の緩和的放射線療法として使用される。

姑息的外科治療

高度進行大腸癌や切除不能大腸癌では，化学療法を行う前に原発巣切除を行うか否かで予後を比較したエビデンスレベルの高い論文は存在しない。化学療法の有効性が認識されるようになり，いかにQOLを保持しながら化学療法を維持できるかが治療成績の向上の鍵となっており，有症状の原発巣切除は考慮されるべきであるが，切除にリスクを伴う場合はストーマ造設術を選択する場合もある。無症状の場合は，有症状となったときの手術リスクも考慮して切除方針を決定すべきである。

術後の注意点

術後管理における要点は，「各種チューブの早期抜去・早期離床・早期経口摂取開始」を実行し「早期回復を達成する」ことである。最近では早期回復が望める腹腔鏡手術で「各種チューブの早期抜去・早期離床・早期経口摂取開始」が達成された。このようなコンセプトは開腹手術にフィードバックされ，「各種チューブの早期抜去・早期離床・早期経口摂取開始」を従来の開腹手術でも積極的に行うようになった。結腸癌手術の注意すべき術後合併症は，腸閉塞・縫合不全・創感染；SSI（surgical site infection）である。術後腸閉塞は腸蠕動の低下と癒着を原因とすることが多く，腹満・腹痛・嘔吐として発症する。術後早期離床をすすめて腸管蠕動を促し可能な限り癒着を減らすことで腸閉塞の予防につとめる必要がある。縫合不全

は吻合した腸の縫合部から便が腹腔内へ漏れるため，腸管蠕動が低下し，腹痛・発熱を認め，腹腔内にドレーンが入っている場合には汚染された排液が観察される。創感染とは創部の皮下に膿瘍を発生することであり，創部の発赤・疼痛・発熱として観察される。結腸癌手術は術中に腸管内容物が術野に曝露される手術であり汚染手術であり，創縁保護目的にAlexis™ wound retoractorなどを使用しても創感染の発生を0％にできない。術後は，バイタルサインのチェック，腹部の観察(視診，聴診)，排便・排ガスの確認は重要である。

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特集 増え続ける大腸癌ー基礎から臨床までー

結腸癌に対する腹腔鏡手術は標準治療となったのか

Laparoscopic operation for colon cancer - Is it standard therapy in Japan?

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大腸癌に対する腹腔鏡手術件数は毎年増加し，進行癌に対しても応用されつつある．海外の臨床試験は腹腔鏡と開腹手術の腫瘍学的同等性を示し，進行癌に対しても腹腔鏡手術は標準治療の一つとなりうることを示した．しかし国内では，JCOG 0404が進行中で結果が出ていないことや難易度の高い横行結腸癌・直腸癌などの腹腔鏡手術の位置づけなど，結腸癌を含む大腸癌に対する腹腔鏡手術が標準療法としての地位を獲得するのにはまだ時間がかかりそうである．

はじめに

腹腔鏡下大腸手術は1991年にJacobsらが世界で初めて紹介し[1]，1993年に渡邊ら[2]，1994年にKonishiら[3]が本邦での腹腔鏡下大腸手術症例を紹介した．腹腔鏡下大腸手術はその低侵襲性や癌に対する手術としての妥当性が徐々に評価され，現在ではさまざまな大腸疾患に対する手術方法として定着しつつある．

I. 標準治療とは

標準治療とは，その時点で最も効果が高いと科学的に証明された治療法のことである．すなわち，医師個人の勘や経験に頼った医療ではなく，大規模な臨床試験によって効果が証明された，その時点で最も成績の良い治療方法である．また，標準治療を定めることの目的の一つは，患者が誰でもどこでも同じように最良の治療を受けることができるようにすることである．このような観点から「結腸癌に対する腹腔鏡手術は標準治療か？」という問いに答えるならば，「ある条件を満たした結腸癌患者にとって腹腔鏡手術は標準治療のひとつである」と答えるのが最も正確な答えではないかと考える．なぜなら，現段階で，大腸癌に対する腹腔鏡手術治療成績は開腹手術治療成績と比較して腫瘍学的に同等であり，決して「最も成績の良い治療方法」ではない．また，誰でもどこでも同じように大腸癌に対する腹腔鏡手術を受けることができるかというとこれもまだ十分ではない．さらに留意すべき最も重要な点は本邦での大腸癌

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