Endoluminal surgery

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SURGICAL ENDOSCOPY
and Other Interventional Techniques

Usefulness of transanal endoscopic surgery for carcinoid tumor in the upper and middle rectum

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Abstract
Background: This study evaluated the indications and outcome for transanal endoscopic surgery (TES) used to manage rectal carcinoid tumor as compared with those of conventional transanal local resection (TAR).
Methods: The retrospective study subjects were 28 patients with rectal carcinoid tumor treated by TES (n = 17) or TAR (n = 11) between January 1995 and December 2001. Patient and tumor characteristics, operative results, and postoperative outcomes were compared between the two groups.
Results: The distance from the anal verge to the distal tumor margin in the TES group (range, 4–12 cm; median, 6.8 cm) was significantly greater than in the TAR group (range, 3–6 cm; median, 4.5 cm) (p = 0.001). The median tumor diameter was 5.5 mm (range, 3–11 mm) in the TES group and 5.0 mm (range, 3–8 mm) in the TAR group, showing no statistical difference. Microscopically, resected specimens in both groups were typical carcinoid tumors restricted to the submucosal layer. No recurrence was noted in either group.
Conclusion: Whereas TES is useful for patients with small rectal carcinoid tumor of typical histology within the submucosal layer in the upper and middle rectum, TAR is effective for accessing the lower rectum.

Key words: Rectal carcinoid — Local resection — TEM — TES

Although carcinoid tumor of the rectum is rare, increasing numbers of rectal carcinoid tumor are being reported [11, 18]. Among the gastrointestinal carcinoid tumors, rectal carcinoid is the second most frequent lesion in the United States and Europe (27.4%) [11] and the most frequent lesion in Japan (36.2%) [18]. The recent marked increases in the number of rectal carcinoids may be attributable to improved endoscopic diagnosis and increased awareness of carcinoid tumors [11].

Local rectal excision is recommended as a curative and minimally invasive treatment for most rectal carcinoid tumors smaller than 2 cm in diameter and restricted to the submucosal layer [6, 20]. Conventional transanal local resection (TAR) often is used to remove a lesion in the lower rectum [14], but other procedures are been required for removal of a lesion in the middle or upper rectum. Thus, transanal endoscopic microsurgery (TEM) was developed by Buess et al. [3] in 1984. Since then, several modified TEMs, such as insufflation video endoscopic TEM (insufflation VTEM) [21] and gasless VTEM [2, 12], have been developed. One Japanese group of TEM researchers has applied the generic term "transanal endoscopic surgery (TES)" to both the original and modified TEM procedure [7]. Recently, TES has been performed worldwide. However, TES for rectal carcinoid tumor has not been evaluated in detail with respect to postoperative results.

We conducted a study aimed at clarifying the usefulness of TES for the treatment of rectal carcinoid tumor. Our approach was to compare TES indications and results with those of TAR for this rectal tumor.

Patients and methods

Between January 1995 and December 2001, 28 patients (11 men and 17 women; average age, 54.4 years; range, 36–70 years) with rectal carcinoid tumor underwent transanal local treatment. Whereas 17 of these patients underwent TES, 11 patients underwent conventional TAR. Their clinical records were reviewed for age, sex, tumor diameter and location, tumor distance from the anal verge to the distal margin of the tumor, central umbilication, operation time, blood loss, postoperative complications, recurrence, and histologic findings.

Treatment in the 28 cases followed the schema shown in Fig. 1. During the study period, no open surgery for this disease was performed. The patients in the TES group had surgery under gen-

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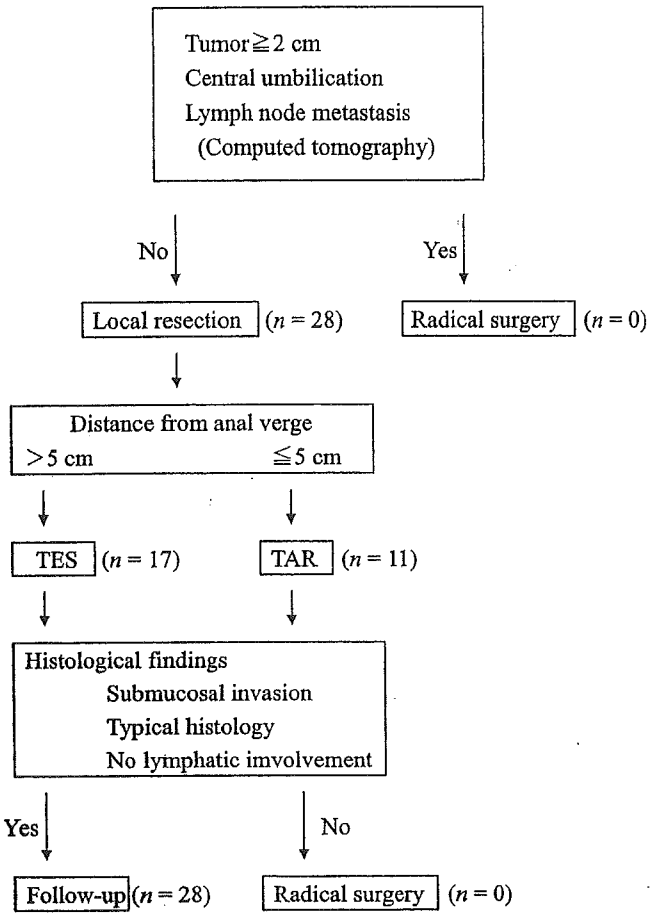

Fig. 1. Strategy for the treatment of rectal carcinoid tumor at the authors' institution as applied to the study patients. TES, transanal endoscopic surgery; TAR, transanal local resection.

eral anesthesia. The TES procedures were performed as described elsewhere [2, 7, 12, 21]. In short, TES is transanal surgical procedure using a rectal tube with a laparoscope. Depending on the tumor location, the lithotomy, prone, or lateral position of the patient was used. Gentle rectal dilation was performed, and a rectoscope tube (length, 12 or 20 cm long; width, 40 mm) was inserted. The scope position was adjusted so that the lesion occupied the center of the field of view. Then the standard 10-mm laparoscope was connected to a video system. The binocular stereoscopic eyepiece system was not used. Carbon dioxide (CO_2) insufflation was used until a needle-tip knife was used to outline a 5-mm margin of normal mucosa circumferentially. Adrenaline 1:100,000 solution was injected into the submucosal layer for lifting of the lesion and hemostasis. The carcinoid tumor was resected in a partial thickness under laparoscope.

The first 3 patients were treated with CO_2 insufflation during the operation (insufflation VTEM [21]), and the 14 subsequent patients were treated without CO_2 insufflation after circumferential marking (gasless VTEM [2, 12]). In the TAR group, the conventional Parks approach [14] was performed with the patients under spinal anesthesia. Park's anorectal retractor was inserted into the rectum and opened to expose the tumor. The carcinoid tumor was resected in a partial thickness, as visualized by the eye. No additional radical surgery was performed in either group.

The patients were examined every 3 months for 2 years after the operation, and every 6 months thereafter. The mean follow-up period was 47.1 months (range, 12–96 months) for the TES group and 23.8 months (range, 6–49 months) for the TAR group. Differences between the groups were analyzed using the Mann–Whitney *U* test or Fisher's exact test as appropriate. A *p* value less than 0.05 was considered statistically significant.

Results

The two groups were comparable in terms of age, sex ratio, and tumor characteristics including size, location, and gross appearance (Table 1). The median tumor diameter was 5.5 mm (range, 3–11 mm) in the TES group and 5.0 mm (range, 3–8 mm) in the TAR group, showing no statistical difference. The distance from the anal verge to the distal tumor margin in the TES group was significantly greater than in the TAR group (Table 1). The distribution of this distance is shown in Fig. 2. In the TES group, the tumors were located 4 to 12 cm from the anal verge, whereas in the TAR group, the tumors were 3 to 6 cm from the anal verge (median, 6.8 vs 4.5 cm).

The operative findings and postoperative courses are shown in Table 2. The mean operation time was greater in the TES group than in the TAR group (86 vs 35 min). Blood loss was minimal for all the patients. The postoperative course was satisfactory except for one patient treated by insufflation TEM in whom retroperitoneal emphysema developed because of a full-thickness excision. However, this complication improved conservatively within 9 days. Three patients in the TES group experienced transient soiling because of the rectoscope tube width (40 mm), but recovered completely within 1 week. The mean follow-up period for all the patients was 38 months (range, 6–96 months). No recurrence or tumor-related mortality was noted.

The pathologic findings for the carcinoid tumors resected by transanal local resection are shown in Table 3. In both groups, microscopic examination showed that all resected specimens were typical carcinoid tumors restricted to the submucosal layer. Carcinoid cells were not seen in the lateral or vertical margin of any specimen. Lymphatic involvement was not observed in any patient. Vascular involvement was noted in only one patient in the TAR group. Ulceration was not observed in any patient.

Discussion

Our results showed TES to be superior to TAR in terms of tumor distance from the anal verge, but inferior to TAR in terms of operation time. The findings showed TES be safe because there was no tumor-related death and no persistent complication. In addition, recurrence was absent. Thus, as with TAR used for the lower rectum, TES is useful for the middle or upper rectum of patients with rectal carcinoid tumor of typical histology confined to the submucosa.

The prognostic factors for rectal carcinoid are reported to be tumor size [6, 10, 16], infiltration of the muscularis propria [10, 16], central umbilication or ulceration of the tumor [6], atypical histology [8, 17], and lymphatic invasion [5]. The incidences of distant metastasis for rectal carcinoid tumors with diameters less than 1 cm, 1 to 2 cm, and exceeding 2 cm are 0% to 3%, 0.4% to 27%, and 45% to 75%, respectively [6, 8, 10, 20]. It has been suggested that a tumor larger than 2 cm

Table 1. Patient and tumor characteristics in the two study groups

	TES (n = 17)	TAR (n = 11)	p Value
Patients			
Age (years)[a]	55 (38–70)	54 (36–69)	NS[b]
Sex ratio (M:F)	8:9	3:8	NS
Tumor			
Size(mm)[a]	5.5 (3–11)	5.0 (3–8)	NS[b]
Location (A/P)	10/7	8/3	NS
Distance from anal verge (cm)[a]	6.8 (4–12)	4.5 (3–6)	0.001[b]
Central umbilication (yes/no)	0/17	0/11	NS

TES, transanal endoscopic surgery; TAR, transanal local resection; A, anterior wall; P, posterior wall; NS, not significant, Fisher's exact test
[a] Values are median (range)
[b] Mann-Whitney U test

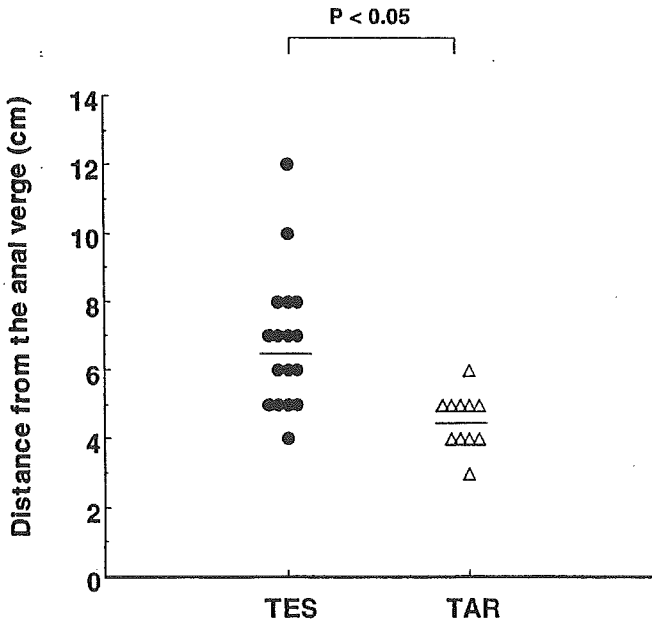

Fig. 2. Distance of rectal carcinoids from the anal verge in the two study groups (solid lines mark the mean distance). TES, transanal endoscopic surgery; TAR, transanal local resection.

in diameter can be regarded as malignant. Previous studies have suggested that complete local resection of a carcinoid tumor is associated with a low rate of local recurrence [6, 15], whereas residual macroscopic disease is associated with a poor outcome [1].

Application of endoscopic resection is not common. Endoscopic mucosal resection is reserved for complete resection of carcinoid tumors because these tumors are sessile and develop from the deep mucosal layer toward the submucosa [9, 13]. However, Stinner et al. [20] reported that radical resection for rectal carcinoid should be performed only after accurate histologic study of a local resected specimen. These authors also indicated that when hematogenous metastasis is absent, radical surgery should be performed for patients with a lesion diameter larger than 2 cm [20]. To the contrary, several authors suggest that radical surgery is inappropriate even if the lesion diameter exceeds 2 cm [8, 15, 16].

Currency, complete local excision is widely accepted for small rectal carcinoids. All the tumors in our study were relatively small (≤ 11 mm) without central umbilication. Postoperative histologic study pointed to a good prognosis for all the patients, and no additional resection was required. To date, there has been no recurrence in any case, and we consider transanal local excision to have been sufficient in all cases. Nevertheless, there have been several reports of malignant potential of tumors smaller than 1 cm [5, 8, 15, 16, 19]. Therefore, even where local excision is indicated, the possibility of metastasis should be taken into account.

Conventional TAR is a useful, minimally invasive procedure for local resection of rectal tumor [14]. However, obtaining sufficient surgical field is sometimes difficult. In addition, TEM can be a useful and safe procedure for rectal tumor, unreachable via the conventional TAR approach. As compared with conventional TAR, TEM provides a superior intraluminal operation field in the middle and upper rectum because the surgical field is broadened by CO_2 insufflation [4]. Although gasless VTEM is slightly inferior to the original TEM with CO_2 insufflation for obtaining a good intraluminal operative field [12], we used gasless VTEM after encountering a patient treated by insufflation VTEM in whom retroperitoneal emphysema developed.

Most rectal carcinoid tumors are located in the middle portion of the rectum [6, 19], and TES is superior to TAR for treating them. Thus, selection of the appropriate treatment depends on the distance from the anal verge to the distal tumor margin: TAR is performed when the distance is 5 cm or less, and TES is performed when it is greater than 5 cm. Digital examination remains the simplest means of determining that distance. The indication for local rectal excision is benign rectal carcinoid tumor that is small (diameter, < 20 mm) and localized within the submucosal layer. Tumors 20 mm in diameter or smaller can be treated effectively using the gasless technique.

In conclusion, TES is safe and useful for patients with a histologically typical small rectal carcinoid tumor that lies within the submucosal layer of the upper or middle rectum.

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Table 2. Operative details and postoperative course in the two study groups

	TES (n = 17)	TAR (n = 11)	p Value
Operative details			
Operation time (min)[a]	86 (45–140)	35 (20–55)	0.001[b]
Blood loss	Minimum	Minimum	NS
Postoperative course			
Complications			
Bleeding	0	0	NS
Stenosis	0	0	NS
Retroperitoneal emphysema	1	0	NS
Recurrence	0	0	NS

TES, transanal endoscopic surgery; TAR, transanal local resection; NS, not significant (Fisher's exact test)
[a] Values are median (range)
[b] Mann-Whitney U test

Table 3. Histologic findings for the two study groups

	TES (n = 17)	TAR (n = 11)	p Value
Histologic type			
Typical/atypical	17/0	11/0	NS
Depth of invasion			
Submucosa/muscularis propria	17/0	11/0	NS
Lateral margin			
Positive/negative	0/17	0/11	NS
Vertical margin			
Positive/negative	0/17	0/11	NS
Lymphatic involvement			
Yes/no	0/17	0/11	NS
Vascular involvement			
Yes/no	0/17	1/10	NS
Ulceration			
Yes/no	0/17	0/11	NS

TES, transanal endoscopic surgery; TAR, transanal local resection; NS, not significant (Fisher's exact test)

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SURGICAL ENDOSCOPY
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Liver metastasis and ICAM-1 mRNA expression in the liver after carbon dioxide pneumoperitoneum in a murine model

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Abstract

Background: Liver metastasis of colorectal malignancies is an important prognostic factor. Several studies have demonstrated that carbon dioxide (CO_2) pneumoperitoneum enhances liver metastasis in animal models. Little is known about intercellular adhesion molecule-1 (ICAM-1) and tumor necrosis factor-alpha (TNF-(α) mRNA expression in the liver after CO_2 pneumoperitoneum.

Methods: Forty-five male BALB/c mice were randomly divided into three groups after intra-splenic tumor cell (colon 26) inoculation and the following procedures were performed: CO_2 pneumoperitoneum (n = 15), open laparotomy (n = 15), and anesthesia alone (n = 15). On day 7 after each procedure, the livers were excised and the number and diameter of the tumor nodules and the cancer index score were determined. Another 90 male BALB/c mice were randomly divided into three groups as described above, and they underwent each procedure (n = 30 each). After each procedure, the livers were excised on days 0, 1, 3, and ICAM-1 and TNF-α mRNA expression were examined by real-time RT-PCR using SYBR Green I.

Results: The number of tumor nodules and the cancer index score were larger in the CO_2 pneumoperitoneum group than in the control group ($p < 0.05$). The mean diameter of the tumor nodules was not different among the three groups. The expression of ICAM-1 in the CO_2 pneumoperitoneum group was higher than that in the other groups on day 1 ($p < 0.05$), and the TNF-α mRNA was higher than that in the control group on day 1 ($p < 0.05$).

Conclusions: CO_2 pneumoperitoneum enhances liver metastasis compared with anesthesia alone, and ICAM-1 expression in the liver after the pneumoperitoneum plays an important role in establishing liver metastasis in a murine model.

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Key words: pneumoperitoneum — Liver metastasis — Adhesion molecules — Murine model — Real-time RT-PCR — ICAM-1

The liver is the most frequent site of tumor metastasis in colorectal carcinoma, and liver metastasis is the most important prognostic factor in patients with primary colorectal cancer. Recently, the use of laparoscopic colorectal surgery has increased because it has become less invasive and because early recovery has become possible. Several randomized controlled trials (RCTs) showed better early short-term outcomes of laparoscopic colectomy [2, 26], but few RCT have been performed with regard to long-term outcomes [16, 17, 24], and the influence of CO_2 pneumoperitoneum on cancer progression is still controversial. In experimental studies, Ishida et al. and Gutt et al. have demonstrated that CO_2 pneurnoperitoneum enhances liver metastasis, and these researchers concluded that hepatic ischemia by CO_2 insufflations may be one of the causes of this phenomenon [7, 8, 10]. Furthermore, previous studies have demonstrated that CO_2 pneumoperitoneum reduces portal blood flow [11, 20, 21].

An important first step in establishing liver metastasis is for free tumor cells to adhere to the hepatic vascular endothelial surface. Yadav et al. have shown that ICAM-1 mediates reperfusion injury in the warm ischemic mouse liver [27]. Alexiou et al. have demonstrated that the serum level of ICAM-1 may reflect tumor progression and metastasis in colorectal cancer patients [1]. However, the expression of ICAM-1 and TNF-α mRNA in the liver after CO_2 pneumoperitoneum has not been clearly established.

In the present study, we investigated the effect of CO_2 pneumoperitoneum and the role of local ICAM–1 expression in establishing liver metastasis in an animal model.

Materials and methods

Animals

All animals were kept under standard laboratory conditions (temperature 20–24°C, relative humidity 50–60%, 12-h light/dark cycle) and were given a standard laboratory diet with free access to water *ad libitum* before and after surgery. All experiments were performed according to the guidelines for animal experimentation of Oita University. This study was performed using a murine pneumoperitoneum model [22]. A total of 135 male BALB/c mice, preserving T- and B-cell immunity, aged 6–8 weeks and weighting 20–24 g, were used. All surgical procedures were performed under ether anesthesia.

Tumor cell line

A mouse colon carcinoma cell line, colon 26 [13, 25], was maintained in RPMI 1640 medium supplemented with 10% fetal bovine serum and penicillin-streptomycin at 1000 IU/ml and incubated in a humidified atmosphere of 95% air and 5% CO_2 at 37°C. For the establishment of liver metastases, tumor cell suspension of 1×10^6 cells/0.1 ml in PBS was used.

Operative procedure

All surgical procedures was done under general anesthesia induced by diethyl ether inhalation. A total of 135 BALB/c mice (including both experiments 1 and 2) were divided into three operative groups. In the pneumoperitoneum group (n = 45), mice were treated with CO_2 pneumoperitoneum at 8–10 mmHg for 60 min as previously reported [10]. Pneumoperitoneum condition was created by following procedure.

(a) A 22-gauge intravenous cannula was inserted into the left lower quadrant and used as an insufflation needle.
(b) A 20-gauge intravenous cannula was inserted into the right lower quadrant and used to measure intraperitoneal pressure.
(c) A disposable syringe to inject the gas was used as the insufflator. A syringe pump was used for continuous insufflation, and intraperitoneal pressure was measured as the distance between the right and left water levels in the U-shaped tube. In the laparotomy group (n = 45), a 3-cm abdominal midline incision was made, and the laparotomy condition was maintained for 60 min. In the control group (n = 45), only diethyl ether anesthesia was performed for 60 min.

Experiment 1 Induction of liver metastasis using a murine intra-splenic tumor cell inoculation model.

Forty-five mice were used in this experiment. A 5-mm skin incision was made at the left back side, and the spleen was pulled out gently. Then, we injected intra-splenically 1×10^6 tumor cells/0.1 ml in PBS using a 30-gauage needle. At 2 min after the tumor-cell injection, the spleen was excised, and the skin was then closed in layers using nonabsorbable interrupted sutures. Immediately after this procedure, the mice were divided into three groups. In the pneumoperitoneum group (n = 15), we administered CO_2 pneumoperitoneum at 10 mmHg for 60 min. In the laparotomy group (n = 15), a 3-cm midline laparotomy was performed and maintained for 60 min. The skin incision was closed by interrupted sutures using 4-0 nylon. In the control group (n = 15), we administered general ether anesthesia for 60 min. All mice were killed on day 7 after each procedure, and we evaluated the numbers, diameter, and cancer index score [7] of metastatic nodules. Each cancer nodule on the liver surface was scored using the cancer index as shown in Table 1, and the total cancer index for each mouse was calculated as the sum of the cancer indices of each nodule.

Experiment 2 Expressions of ICAM-1 and TNF-α mRNA in the liver

Ninety mice were randomized and divided into three groups: the pneumoperitoneum group, the open laparotomy group, and the control group (n = 30 each). Each operative procedure was performed by the same methods used in Experiment 1. After each procedure, the animals' livers were excised on days 0, 1, and 3, snap-frozen in liquid nitrogen, and stored at −80°C until total RNA was extracted. Total mRNA was isolated from the liver by the acid guanidinium thiocyanate–phenol–chloroform extraction procedure [3]. The cDNA was synthesized by reverse transcription from 2.5 μg of total RNA. The cDNA specific for ICAM-1, TNF-α, was measured by PCR. The mRNA of β-actin was measured as the internal control. All PCR reactions were measured by a real-time PCR method using the Light Cycler System (Roche Diagnostics, Mannheim, Germany), and the detection was performed by measuring the binding of the fluorescent dye SYBR Green I to double-stranded DNA. The PCR reactions were set up in microcapillary tubes in a total volume of 20 μl. A master mix of the following reaction components for ICAM-1 and β-actin was prepared to the indicated final concentration: 8.6 μl water, 2.4 μl $MgCl_2$, 1 μl forward and reverse primers, and 2 μl Light Cycler Fast Start DNA Master SYBR Green I (Roche, Mannheim, Germany). A master-mix of the following reaction components for TNF-α was prepared to the indicated final concentration: 9.4 μl water, 1.6 μl $MgCl_2$, 1μl forward and reverse primers, and 2 μl Light Cycler Fast Start DNA Master SYBR Green I. Table 2 presents an overview of primer sequences and factor-specific amplification conditions with the single fluorescence measurement were used in this study. The following general real-time PCR protocol was used: a denaturation program (95 °C for 10 min), followed by an amplification program that was repeated 40 times (Table 2), a melting curve program (60–99°C with a heating rate of 0.1°C /sec and continuous fluorescence measurements), and finally a cooling program down to 40°C. The PCR product sizes for ICAM-1, TNF-α, and β-actin were 326 bp, 349 bp, and 189 bp, respectively. The relative fluorescence of each mRNA was normalized to that of β-actin for semiquantification.

Table 1. Cancer index scoring dependent on the diameter

Cancer index (score)	Diameter of nodule (mm)
1	< 5
2	5–10
3	> 10

Statistical analysis

Data were expressed as mean ± standard deviation (SD). Differences between the mean of the control group and those of the treatment group were evaluated by analysis of variance (ANOVA) followed by the Tukey HSD multiple comparison test. The differences between the groups were regarded as significant when $p < 0.05$. All statistical calculations were performed using the Dr. SPSS (version 11.01) program for Windows computers.

Results

Experiment 1

The number of metastatic nodules was greater in the CO_2 pneumoperitoneum group than in the control group (15.82 ± 5.69 vs 8.80 ± 6.80, $p < 0.05$) (Fig. 1). However, the mean diameter of the tumor nodules was not significantly different among all groups (Fig. 2). The total cancer index in the CO_2 pneumoperitoneum group was higher than that in the control group (26.00 ± 9.76 vs 13.70 ± 11.26, $p < 0.05$) (Fig. 3). Both the number of metastatic nodules and the total cancer index were not significantly different between the CO_2 pneumoperitoneum group and the laparotomy group.

Table 2. Sequences of primers used for RT-PCR and amplification conditions with a single fluorescence measurement

Molecule		Primer sequence (5′–3′)	Real-time PCR cycling conditions (sec/°C)		
			Denaturation	Annealing	Elongation
β-actin	Sense	TGG-AAT-CCT-GTG-GCA-TCC-ATG-AAA-C	15/95	10/55	14/72
	Antisense	TAA-AAC-GCA-GCT-CAG-TAA-CAG-TCC-G			
ICAM-1	Sense	TGC-GTT-TTG-GAG-CTA-GCG-GAC-CA	15/95	10/60	13/72
	Antisense	CGA-GGA-CCA-TAC-AGC-ACG-TGC-CAG			
TNF-α	Sense	CCA-CGT-CGT-AGC-AAA-CCA-C	10/95	10/60	7/72
	Antisense	TGG-GTG-AGG-AGC-ACG-TAG-T			

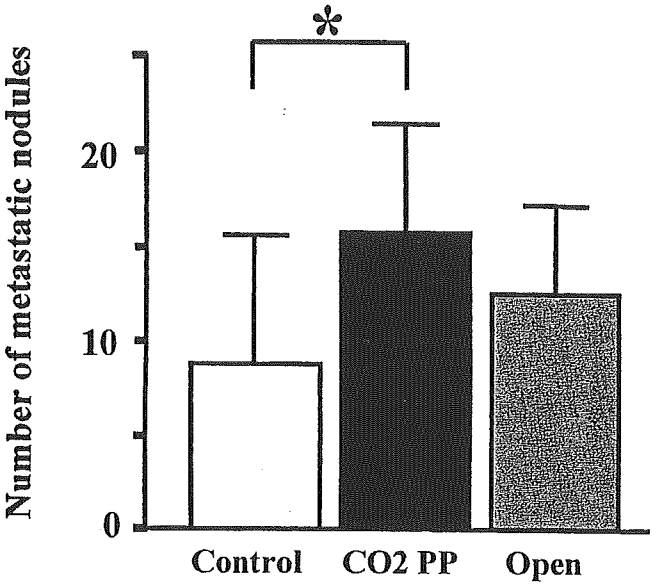

Fig. 1. The number of metastatic nodules on the liver surface was significantly greater in the CO_2 pneumoperitoneum group than in the control group. PP, pneumoperitoneum (*$p < 0.05$).

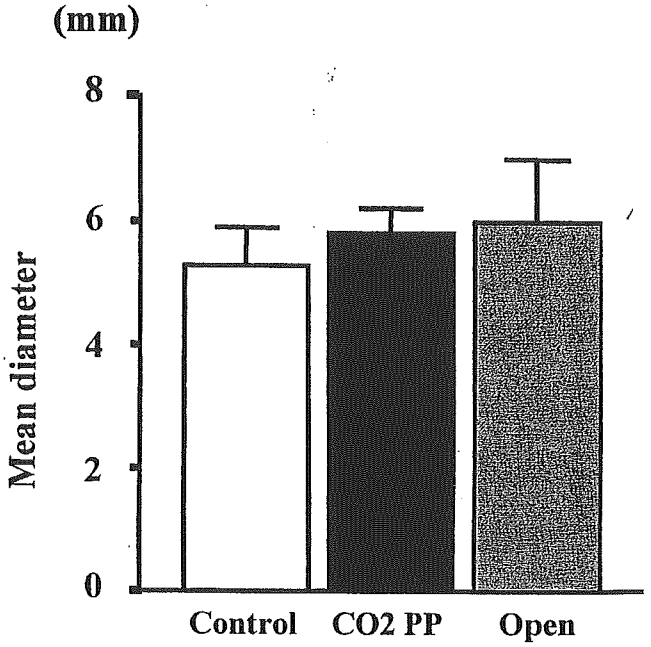

Fig. 2. The mean diameter of metastatic nodules was not significantly different among any of the groups.

Experiment 2

The expression of ICAM-1 mRNA in this study is shown in Fig. 4a. On day 0 (immediately after each procedure), the expression of ICAM-1 mRNA was not significantly different among the groups. On day 1, the expression of ICAM-1 mRNA was higher in the CO_2 pneumoperitoneum group than in the control and the open group (1.86 ± 0.56 vs 0.59 ± 0.42, 1.14 ± 0.40, $p < 0.05$). On day 3, the expression of ICAM-1 mRNA was higher in the CO_2 pneumoperitoneum and laparotomy groups than in the control group (2.03 ± 0.79, 1.62 ± 0.71 vs 0.74 ± 0.35, $p < 0.05$).

The expression of TNF-α mRNA in the CO_2 pneumoperitoneum group was higher than that in the control group on day 1 (0.177 ± 0.078 vs 0.025 ± 0.031, $p < 0.05$) (Fig. 4b). On days 0 and 3, there were no significant differences among any of the groups.

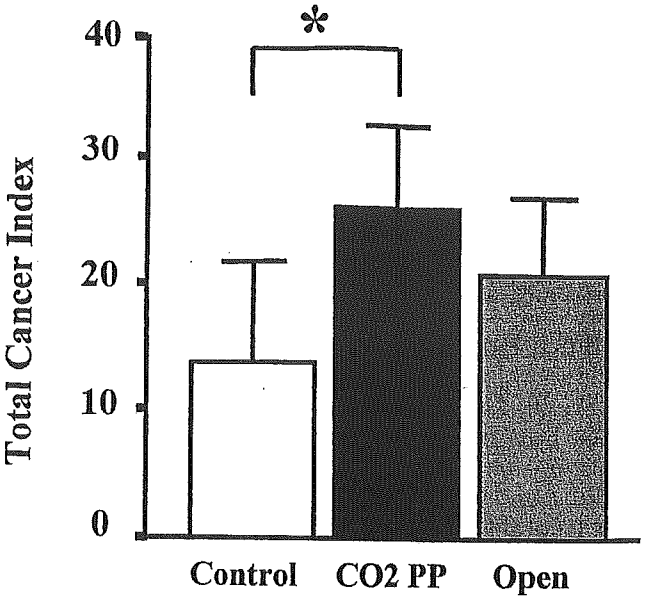

Fig. 3. The total cancer index score was significantly greater in the CO_2 pneumoperitoneum group than in the control group (*$p < 0.05$).

Discussion

In the present study, we examined the effect of CO_2 pneumoperitoneum on liver metastasis from the view-

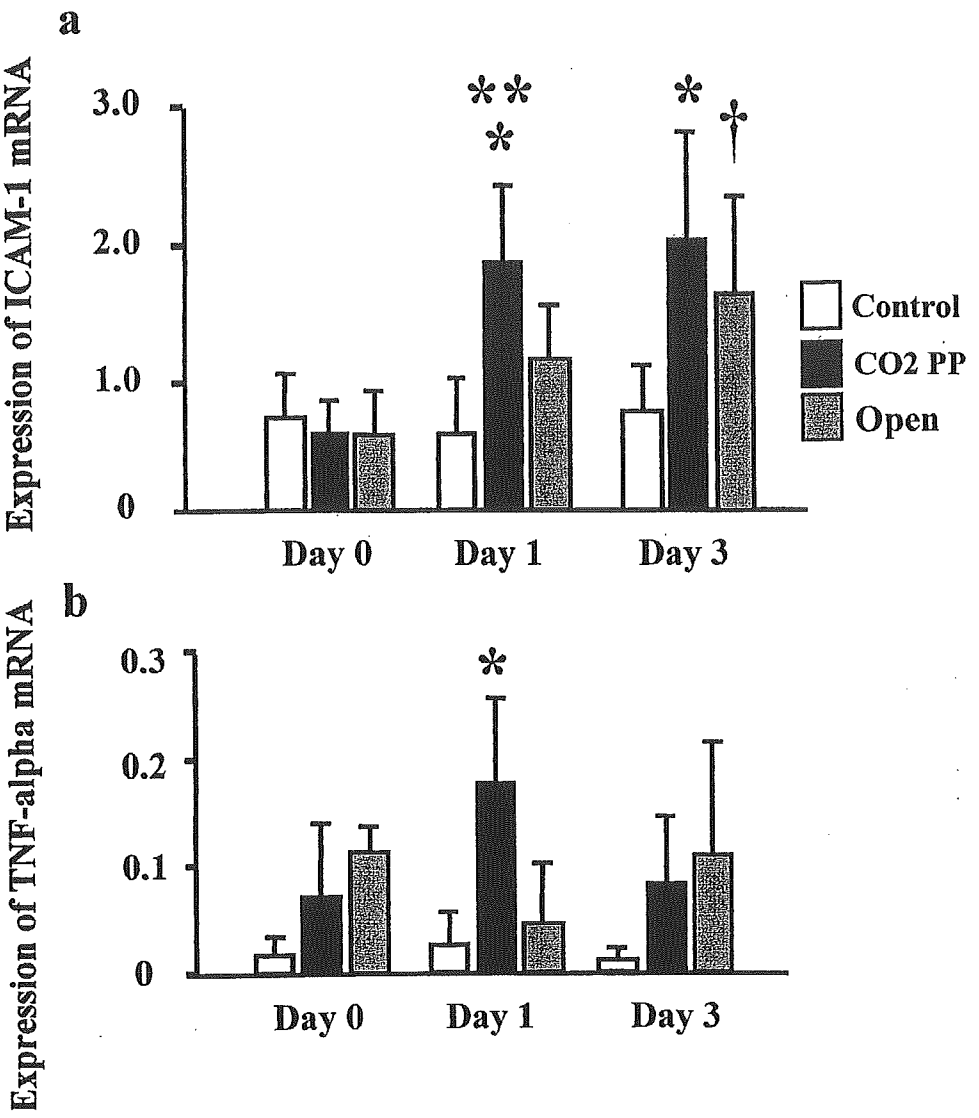

Fig. 4. a Expression of ICAM-1 mRNA and b TNF-α-mRNA in the liver measured by real-time RT-PCR. The relative expression of each mRNA is normalized to the expression of β-actin for semi-quantification. $p < 0.05$ CO_2 pneumoperitoneum versus control group, $^{**}p < 0.05$ CO_2 pneumoperitoneum versus open group, $\dagger p < 0.05$ laparotomy versus control group.)

points of intrahepatic adhesion molecule expression using a murine liver metastasis model. Our results showed that both the number of tumor nodules on the liver surface and the cancer index score were higher in the CO_2 pneumoperitoneum group than in the control group. The intrahepatic expression of ICAM-1 was higher in the CO_2 pneumoperitoneum group than in the other groups. Thus, in a murine model, CO_2 pneumoperitoneum enhanced liver metastasis, and the induction of ICAM-1 after CO_2 pneumoperitoneum may play an important role in the establishment of liver metastasis.

The first step in the establishment of liver metastasis is the adherence of free tumor cells to the hepatic vascular endothelium. Several studies have previously demonstrated that intrabdominal insufflation of CO_2 causes a marked and rapid decrease (35% to 84%) in portal blood flow [11, 20, 21]. In this study, portal blood flow may decrease because of the high pressure of CO_2 pneumoperitoneum, which was used in the previous study [10]. Doi et al. demonstrated that the condition of the ischemic lobe is favorable for liver metastasis [5], and the expression of adhesion molecules located in the vascular endothelium may play a crucial role in the establishment of liver metastasis. Our results showed an enhancement of liver metastasis and an increase of ICAM-1 and TNF-α after CO_2 pneumoperitoneum. It is possible that CO_2 pneumoperitoneum causes damage to the hepatic vascular endothelium by inducing liver ischemia.

ICAM-1 is a member of the immunoglobulin supergene family of adhesion molecules. Previous studies have demonstrated that ICAM-1 mediates hepatic reperfusion injury in the ischemic mouse liver [15, 27, 28]. Taketomi et al. demonstrated that the enhancement of inflammation in the liver is related to intrahepatic recurrence through ICAM-1 in patients with hepatocellular carcinoma [23]. The expression of ICAM-1 can be upregulated by inflammatory cytokines such as TNF-α and interleukin-1 [4, 18]. TNF-α is one of the most effective cytokines for inducing the expression of ICAM-1 on the endothelial cells [14, 19]. Gulubova et al. concluded that the enhanced expression of adhesion molecules in the liver sinusoids could direct the adhesion of new circulating tumor cells to the sinusoidal endothelium [6]. Kamei et al. demonstrated that TNF-α mRNA expression in the liver is higher 3-24 h after air pneumoperitoneum than after anesthesia alone [12]. In the

present study, we demonstrated the increases of ICAM-1 and TNF-α mRNA expression in the liver after CO_2 pneumoperitoneum. Also, the peak of TNF-α mRNA expression appeared earlier than that of ICAM-1 after CO_2 pneumoperitoneum. These results suggested that CO_2 pneumoperitoneum caused liver ischemia, and enhanced the expression of ICAM-1 induced by inflammatory cytokines such as TNF-α on the hepatic endothelium. Furthermore, the possibility that new circulating tumor cells adhered to the sinusoidal endothelium via ICAM-1 was shown.

Recently, in a clinical setting, randomized controlled trials regarding the long-term outcome after laparoscopic colorectal cancer surgery were reported [16, 17, 24]. A Spanish trial showed that the cancer-related survival rate in patients with stage III tumors was higher in the laparoscopic group than in the open group [16]. On the other hand, trials in the United States and Hong Kong showed that there were no significant differences in the survival rate between these two groups [17, 24]. In this experimental study, there were no significant differences in the incidence of liver metastasis between the CO_2 pneumoperitoneum group and the laparotomy group. However, we demonstrated that CO_2 pneumoperitoneum enhanced liver metastasis in comparison with the control group, and also that this effect might be associated with the induction of ICAM-1 and TNF-α in establishing liver metastasis. For the inhibition of liver metastasis after CO_2 pneumoperitoneum, it may be necessary to prevent portal blood flow depression by means of a gasless procedure or lower insufflation pressure [9, 10].

In conclusion, in a murine model, CO_2 pneumoperitoneum increased the expression of ICAM-1 and TNF-α in the liver and enhanced liver metastasis compared with anesthesia alone. Further investigation is necessary to clarify the mechanism and established a prevention method of liver metastasis after CO_2 pneumoperitoneum.

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特集 コンセンサス 胃癌の治療 2005~2007

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へるす出版

3 胃癌の外科治療

(1) 腹腔鏡下手術と縮小手術

大分大学医学部消化器外科
北野 正剛／白石 憲男
Seigo Kitano／Norio Shiraishi

はじめに

診断技術の向上や検診制度の普及により，いまや胃癌の約50～60％が早期胃癌として発見される。早期胃癌のリンパ節転移率は低く，m癌2～5％，sm癌15～20％であり，転移があったとしても，ほとんどが胃周囲のリンパ節に限局している。このような早期胃癌に対し，無意味な拡大リンパ節郭清を避け，郭清を必要十分な範囲にとどめる縮小手術が実践されている。

一方，低侵襲手術，すなわち患者にやさしい手術として胃癌治療に導入された腹腔鏡下手術は，『胃癌治療ガイドライン』では臨床研究として位置づけられており，今後の普及・発展が期待されている。

本稿では，腹腔鏡下手術の中でもリンパ節郭清を伴う胃切除術を中心にその適応・手技・現状と問題点について述べる。

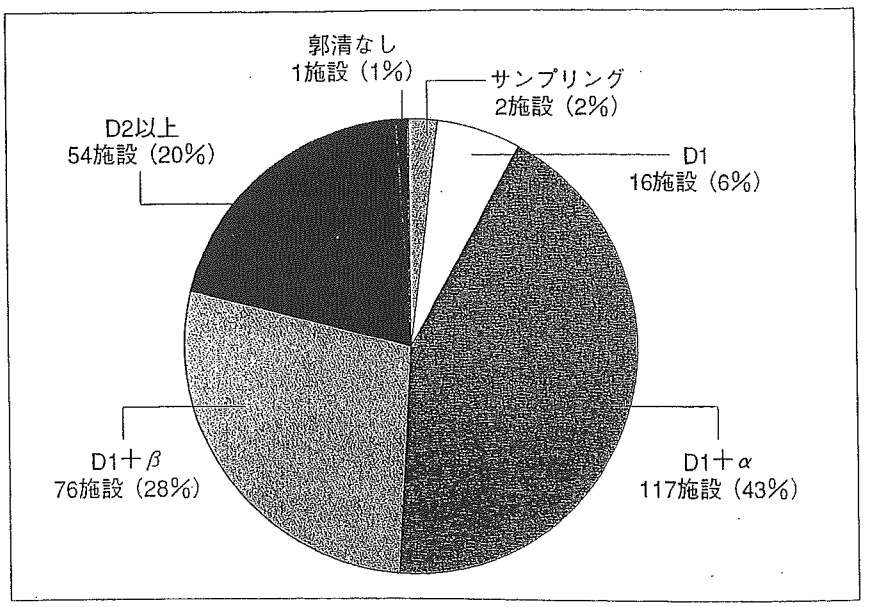
適　応

2004年4月に改訂された日本胃癌学会による『胃癌治療ガイドライン』では，腹腔鏡下手術は縮小手術と位置づけられ，日常診療の適応として早期胃癌に限っている(表1)[1]。これは，手技の安全性や長期成績がまだ十分示されていないためと思われる。日本内視鏡外科学会(JSES)の第7回アンケート調査結果によると(図1)，約79％の施設でD1＋βまでの郭清範囲にとどめており，D2リンパ節郭清を行っている施設は約20％であった[2]。しかしながら，手技の安定化に伴って適応が拡大する傾向にあり，前述のガイドラインでも臨床研究とし

表1　早期胃癌に対する治療

〔文献1）より引用〕

T1（M）	N0	N1
T1（SM）	ＩA EMR（一括切除） （分化型，2.0cm以下， 陥凹型ではUL（－）） 縮小手術A（上記以外）	ＩB 縮小手術B （2.0cm以下） 定型手術 （2.1cm以上）
	ＩA 縮小手術A （分化型，1.5cm以下） 縮小手術B（上記以外）	



〔文献2）より引用〕

図1　リンパ節郭清度

て進行癌T2N0，T2N1までを適応としている。

手　技

リンパ節郭清を伴う腹腔鏡補助下幽門側胃切除術(LADG)は1991年に始まった[3]。そのLADG(D1＋α)の一般的な手順は，腹腔鏡下操作にて①大網・胃結腸間膜を脾下極まで切開しつつ左胃大網動静脈を切離，②胃結腸間膜を切開し膵頭部を露出，③右胃大網静脈を根部にて切離(No.6リンパ節郭清，図2)，④胃十二指腸動脈を同定し右胃大網動脈を根部で切離，⑤十二指腸球部上方の無血管野からのアプローチにて右胃動静脈根部を同定し切離(No.5リンパ節郭清，図3)，⑥小網を切離し，胃膵間膜を切開，⑦左胃動静脈を同定し切離(No.7リンパ節郭清，図4)，⑧No.1，3リンパ節郭清，⑨腹腔鏡下操作が終了した後，剣状突起下(肥満例などではやや右側)に約5cmの小開腹，⑩小開腹創からの操作にて，直視下に，幽門側胃切除，⑪通常Billroth-Ⅰ法による再建，⑫再気腹の後，止血確認・洗浄，である。

LADGは急速に普及し，現在では噴門側胃切除術，胃全摘術などが行われるようになってきた。また，リンパ節郭清もD1＋αからD1＋βやD2へとより根治性を求める方向に向かっている。さらに腹腔内吻合，Roux-en Y吻合など，種々の手技の工夫が図られている。

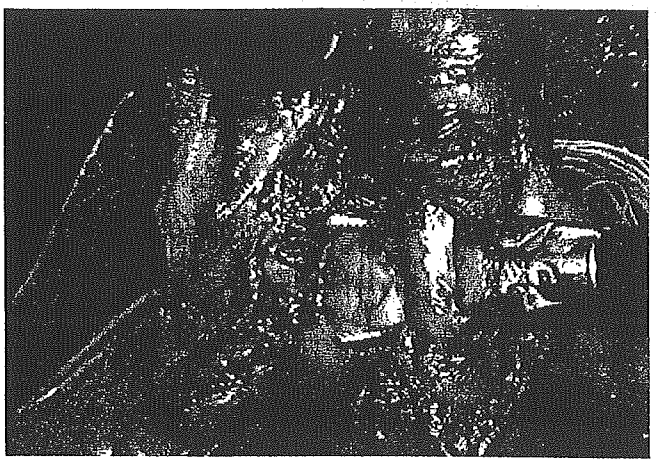


図2

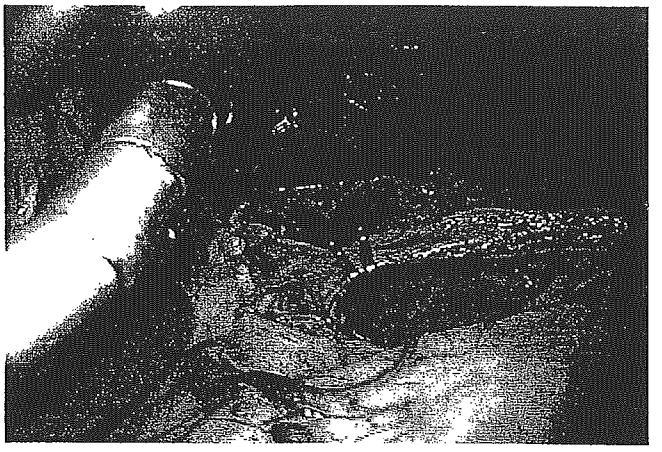


図3

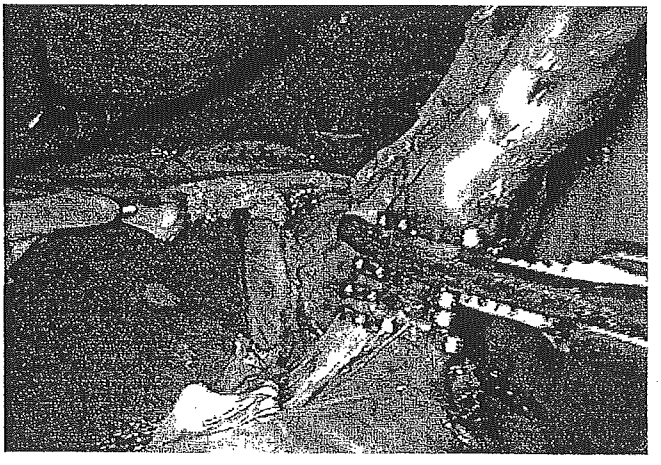
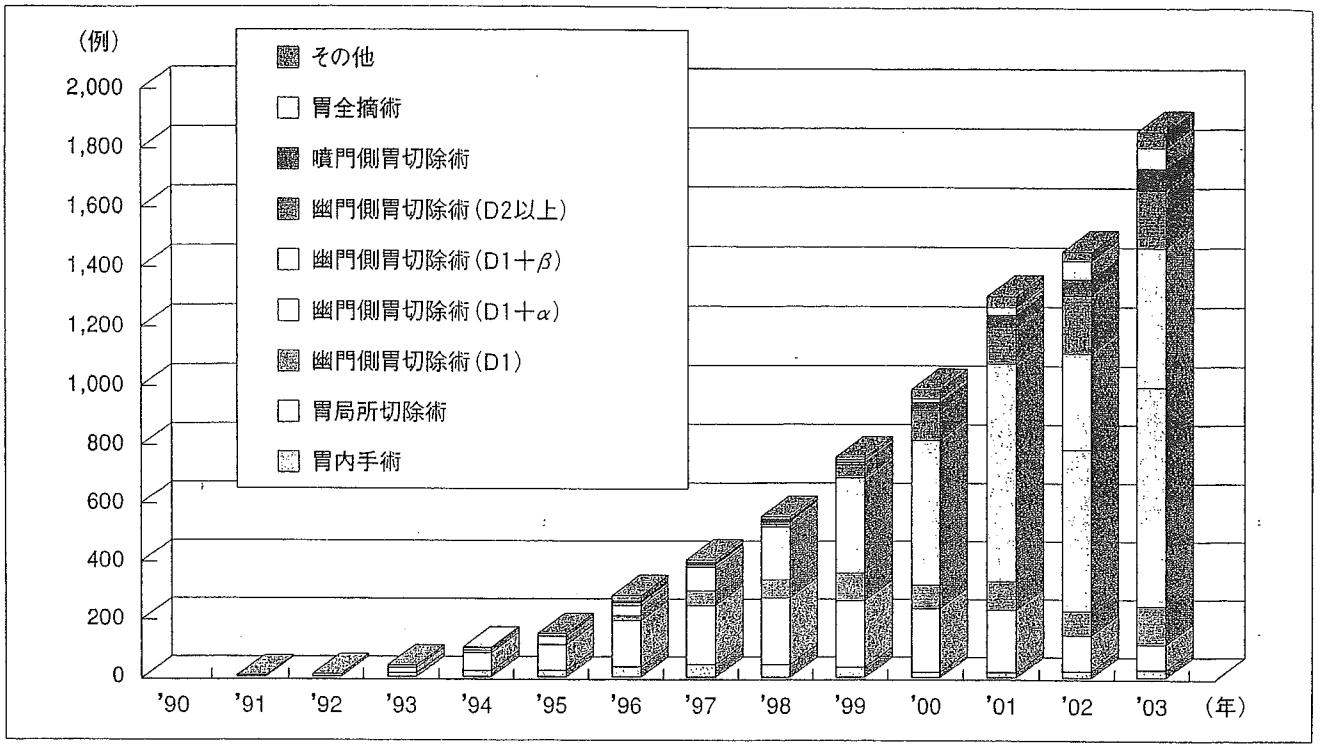


図4

現状と問題点

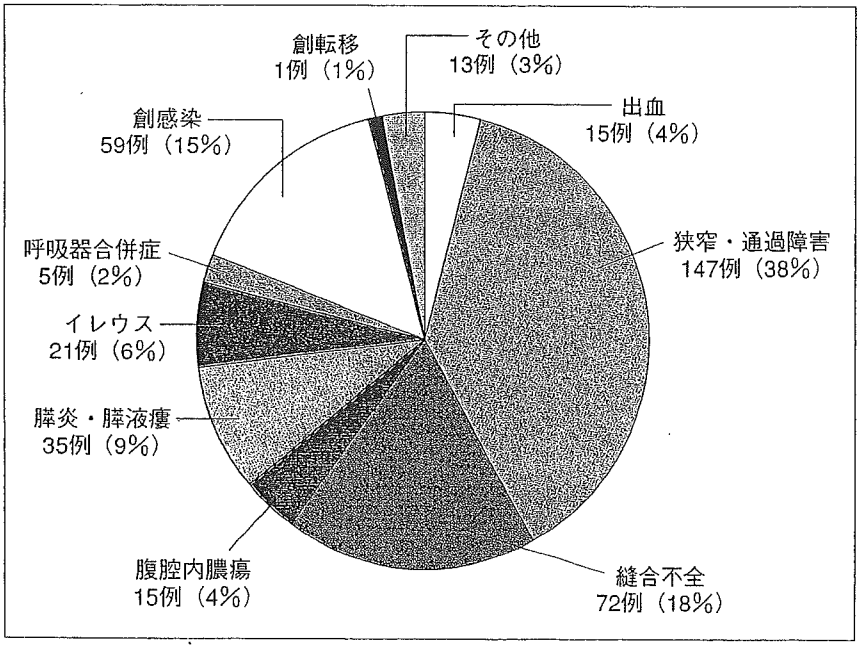
A. 現状

アンケート調査結果によると，1991年から2003年12月までに約7,800例の胃癌症例に腹腔鏡下手術が行われている(図5)。その中で，リンパ節郭清を伴うLADG症例がもっとも多く，次いでリンパ節郭清を伴わない胃局所切除術である。前述のごとく，LADGのリンパ節郭清範囲は，約43％の施設でD1＋α，約28％の施設でD1＋βの郭清が行われており，D2リンパ節郭清は約20％の限られた施設で行われているのが現状である。厚生労働省がん研究助成金研究班(北野班)の調査結果から，No.6と2群リ



〔文献2）より引用〕

図5　胃癌に対する内視鏡外科手術



〔文献2）より引用〕

図6　術後合併症

ンパ節郭清が手技的にも難しいと考えている施設が多く，さらに安全な手技の確立が望まれている[4]。

B.　安全性

同じく全国アンケート調査結果から術中偶発症の発生頻度は1.8%，開腹移行率は1.0%であることがわかる。偶発症の内訳は70%が出血であり，次に他臓器損傷が21%を占めていた。厚生労働省がん研究助成金研究班（北野班）の検討では，出血部位として多いのは左胃動脈と脾門部の静脈であった。

一方，JSESのアンケート調査結果によると術後合併症は7.3%であった。その内訳は，図6のごとく吻合部狭窄・通過障害（38%）や縫合不全（18%）のような吻合部に関するものが半数以上を占めていた。続いて創感染，膵炎・膵液瘻の順であった。しかしながら，これらの頻度は従来の開腹手術と比べ，けっして高い値ではないと思われる。

C.　根治性

厚生労働省がん研究助成金研究班（北野班）での検討の結果，無再発5年生存率は早期癌で99%以上，進行癌（T2N0，T2N1）症例で90%以上と良好な結果であった。これらのデータは，経過観察期間が23カ月と短くその評価は今後のさらなる検討を待たなければならない。

D.　有用性

これまで，短期成績の解析によ

表2 LADGの評価 〔文献5）より引用・改変〕

報告者		症例数 (LADG/DG)	有用性					
臨床経過			早期経口・排ガス	早期歩行	疼痛軽減	術後臓器障害軽減	在院日数軽減	その他
[RCT]								
Kitano S	(2002)	14/14			○	○		
[Case-controlled]								
Adachi Y	(2000)	49/53			○		○	栄養・炎症
Yano H	(2001)	24/35	○	○	○		○	
Reyes CD	(2001)	18/18	○				○	
Mochiki E	(2002)	24/31	○				○	合併症
Migo S	(2003)	10/17	○					炎症
Weber KJ	(2003)	12/13	○				○	
術後免疫								
Fujii K	(2003)	10/10	細胞性免疫の維持					
患者QOL								
Goh PMY	(1997)	16外科医	10人の外科医が患者QOLの向上に有用					
Adachi Y	(1999)	41/35	24項目の消化器症状に関する患者アンケート中，4項目で良好					
費用								
Adachi Y	(2001)	48/43	在院期間短く，総医療費が安価					

る有用性の検討がなされてきた。表2に主な研究結果をまとめたが，1つを除いてすべて症例対象研究であり，質の高い研究とはいいがたい[5]。LADGの低侵襲性という点では，早期排ガス・早期経口摂取，術後疼痛の軽減の点で有用であり，術後在院日数の短縮が可能であったという報告が多い。また，患者アンケートや担当医師へのアンケートによる評価も良好であった。

おわりに

胃癌に対する腹腔鏡下手術は，これまで主に早期胃癌を対象に行われ，その短期成績ならびに長期成績が検討され，有用な手術であることがわかってきた。いまや，早期胃癌に対する腹腔鏡下手術はわが国の先端施設において標準的治療としてのコンセンサスを得た感がある。しかしながら，胃癌全体としてみると腹腔鏡下手術が標準的治療となるためには，多施設研究によるRCTが必要不可欠であると考えている。

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SURGICAL ENDOSCOPY
and Other Interventional Techniques

The author replies

We thank Dr. Huscher and colleagues for the insightful response to our review and for the clinical outcome data for the 56 patients with advanced gastric cancer treated successfully by laparoscopic total or subtotal gastrectomy with D1 and D2 lymph node dissection. The outcome is very interesting and informative for laparoscopic surgeons.

Our review dealt with laparoscopic surgery solely for early gastric cancer because of its demonstrated efficancy in such cancers [3]. Application of laparoscopic gastrectomy with D2 node dissection for advanced cancer remains controversial in Japan where the standard open operative techniques for advanced gastric cancers have long been established. A survey conducted by the Japan Society for Endoscopic Surgery revealed that D2 lymph node dissection was performed in 23% of 2600 laparoscopic gastrectomies between 1991 and 2001 [2]. Laparoscopic surgery was indicated for cancer with a fairly high risk of lymph node metastasis, such as those with massive submucosal invasion, and for advanced cancers remaining in the gastric wall. There is a known increased risk of recurrence such as peritoneal dissemination or port-site metastasis after laparoscopic gastrectomy for advanced cancer, but the effect of laparoscopic surgery on tumor growth and peritoneal dissemination has not been well documented.

There are several reports regarding the outcome of laparoscopic gastrectomy for advanced cancers [1]. Nevertheless, because of the insufficient number of patients and follow-up periods, it is quite difficult to adequately evaluate the outcome of laparoscopic gastrectomy for advanced cancer at the present time.

The excellent results shown by the Italian group suggest that laparoscopic gastrectomy is feasible for the treatment of advanced cancer as well as early cancer. However, a definite conclusion regarding the application of laparoscopic surgery for advanced gastric cancers awaits the accumulation of data regarding laparoscopic surgery in cases of advanced cancer, preferably obtained through multicenter randomized controlled trials.

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縮小手術
腹腔鏡下手術

Laparoscopic gastrectomy for early cancer

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●要旨●早期胃癌に対する腹腔鏡下手術は，1991年にわが国で始められた。多くの施設では腹腔鏡下胃局所切除から導入され，現在D1＋αやD1＋βのリンパ節郭清を行う腹腔鏡補助下胃切除術（LADG）が主体となっている。これまでの14年間に安全な術式の普及がなされ，その結果，良好な短期成績が示されている。しかしながら，長期成績に関しては報告も少なく，まだ臨床研究としての位置を脱却していない。腹腔鏡下手術が胃癌の標準手術となるためには，安全で簡便な手技の確立，低侵襲性などの有用性の評価，さらには癌の手術としての根治性の評価が不可欠である。

● key words：胃癌，腹腔鏡下手術，腹腔鏡補助下幽門側胃切除術

はじめに

早期胃癌に対する手術として1991年にわが国で最初に行われた腹腔鏡補助下幽門側胃切除術（LADG）[1]は，この14年の間に急激に普及してきた。この間，早期胃癌に対する手術として，LADGのみならず，腹腔鏡下胃楔状切除術[2]，腹腔鏡下胃内粘膜切除術[3]など新しい腹腔鏡下手術がわが国で開発された。このような発展は，早期胃癌の発見率の上昇や術後患者QOLの向上を重視する社会背景に支えられている。その結果，2002年にはLADGが保険収載され，第2版の『胃癌治療ガイドライン』[4]にも有望な縮小手術として臨床研究の対象と位置づけられている。

このように急速な普及を示している腹腔鏡下手術が，今後臨床研究から標準手術として位置づけられるためには，いくつかの克服しなければならない課題がある。本稿では，早期胃癌に対する腹腔鏡下手術の現状と問題点について述べる。

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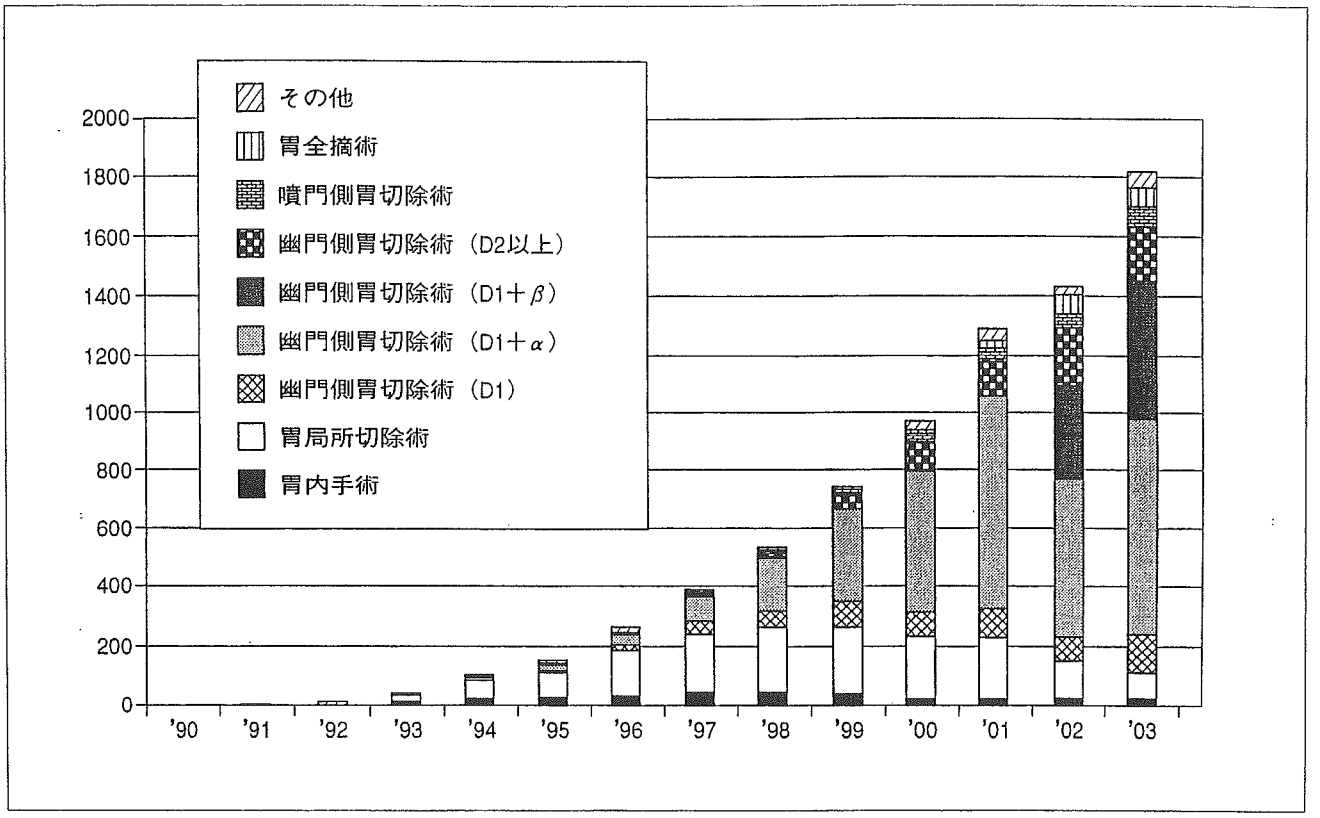
早期胃癌に対する腹腔鏡下手術の現状とその役割

早期胃癌に対する腹腔鏡下手術を，①リンパ節郭清を行わない手術と，②リンパ節郭清を行う手術，の2つに分けることができる。

1. リンパ節郭清を行わない手術

代表的な術式として腹腔鏡下胃楔状切除術と腹腔鏡下胃内粘膜切除術があげられる。これらの術式は，リンパ節転移の危険性がないと判断されながら，手技的にEMRでの一括切除が困難な病変を対象としている。すなわち，大きな病変（1.5cm以上）やEMRの難しい局在（噴門近傍，幽門近傍）に存在する病変がもっともよい適応と考えられる。日本内視鏡外科学会（JSES）の第7回全国アンケート調査結果（図1）[5]に示されるように，腹腔鏡下手術の導入を本術式から始めた施設が多く，1995年前後には腹腔鏡下胃切除術の大半を占めていた。しかしながら，EMRの発展や内視鏡的粘膜剝離法（ESD）の開発により，その適応症例数は減少している。現在進められているセンチネルリンパ節検索の妥当性が認められ，幅広く普及すれば今後本術式が増加する可能性があると思われる。



〔文献5）より引用〕

図1　胃癌に対する内視鏡外科手術

2.　リンパ節郭清を行う手術

1990年代後半から，リンパ節郭清を行うLADGが急速に普及している。これは，超音波凝固切開装置などの機器の開発や外科医の修練により，複雑な腹腔鏡下手術が比較的容易に行うことができるようになったためと思われる。最初はD1＋αのリンパ節郭清が主流であったが，近年ではD1＋βのリンパ節郭清が増加している。また，腹腔鏡下にD2リンパ節郭清を行っている施設も約20％を占めており，T1N0病変からT1N1，T2N0病変に適応拡大している施設もある。一方，術後患者QOLの向上を目的とし，噴門側胃切除術，幽門温存術式，迷走神経温存術式などを腹腔鏡下に行う試みもなされている。今後，臨床研究としての位置を脱却し標準術式に定着するためには，より安全で簡便な手技の確立，腫瘍学的立場からの評価が必要である。

手　技

腹腔鏡下胃切除術のなかでもっとも頻度の高いLADG（D1＋βリンパ節郭清）は，腹腔鏡下操作と小開腹創からの操作からなる[6]。

1.　腹腔鏡下操作

臍下部よりオープン法にて腹腔鏡を挿入し，腹腔鏡観察下に上腹部に4本のトロッカーを留置し，手術を開始する。

1）　大網の処理（図2）

助手鉗子との協調操作により，大網を脾臓下極まで切開する。この際，網嚢側に左胃大網動静脈が同定される。クリップ処理の後，超音波凝固切開装置を用いて切離する。大網処理の右側は，十二指腸結腸間膜前葉を十二指腸下行脚の左側縁まで切離しておく。

2）　右胃大網動静脈の切離

右胃大網静脈の根部の同定に際しては，膵頭部前面を十分露出させ，膵前面，中結腸静脈を指標にすると比較的容易に同定することができる。膵損傷を生じないように注意しながらクリップ処理の後，超音波凝固切開装置を用いて切離する。右胃大網動脈の根部の同定は，胃十二指腸動脈を幽門下のほうに剝離を進めることがコツである。右胃大網動脈の剝離に際して，十二指腸側に幽門下動脈の枝が存在するので，剝離鉗子の使用を慎重に行う（図3）。静脈同様にクリップ処置を行った後，超音波凝固切開装置にて切離する。

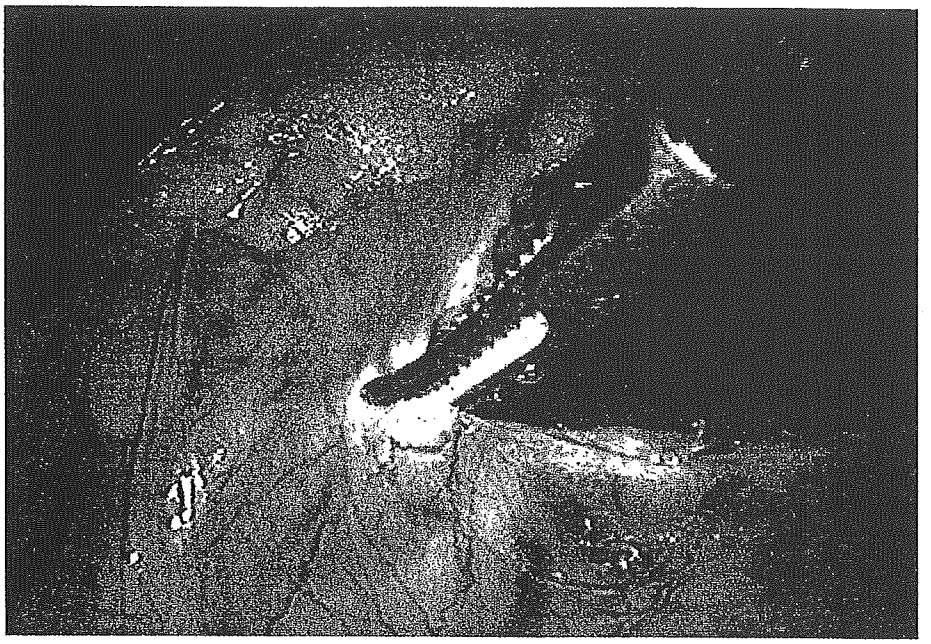


図2

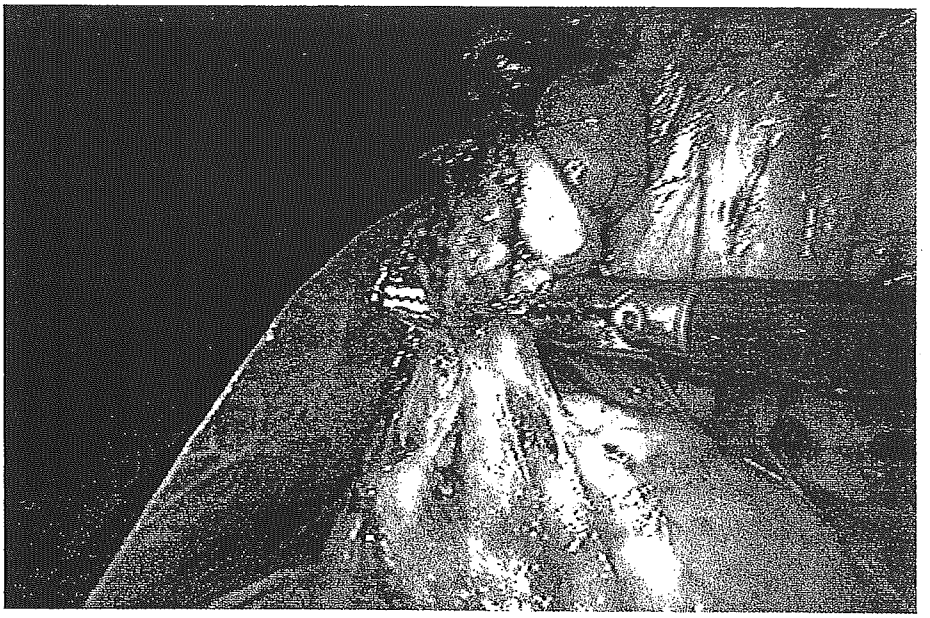


図3

3) 右胃動静脈切離

右胃動脈の根部へのアプローチは二通りある。一つは，十二指腸球部頭側の無血管野を開放し，右胃動脈右側を露出し根部を同定する方法。もう一つは，胃十二指腸動脈から固有肝動脈を露出していき，右胃動脈の根部を同定する方法である。クリップ処理した後，超音波凝固切開装置にて切離する。

4) No. 8 a リンパ節郭清

小網を食道胃接合部まで切開した後，胃十二指腸動脈から総肝動脈の方向に剝離を進め，No. 8 a リンパ節を郭清していく。この際，剝離鉗子を用い膵上縁の剝離層を確認し超音波凝固切開装置で腹膜を切離，頭側へNo. 8 a を剝離する。胃小彎が短く，総肝動脈の観察が不十分な際には，リニアーカッターで十二指腸を切離しておくとよい。

5) 左胃動静脈の切離

No. 8 a リンパ節郭清の際に行った頭側の腹膜切開線を右横隔膜脚に沿って食道胃接合部まで延長しておく。また，膵上縁の切開は胃膵間膜を越えるところまで切離しておく。このように腹膜を切開すると比較的容易に左胃動静脈の根部が同定される。他の血管処理同様，クリップ処置の後，超音波凝固切開装置にて切

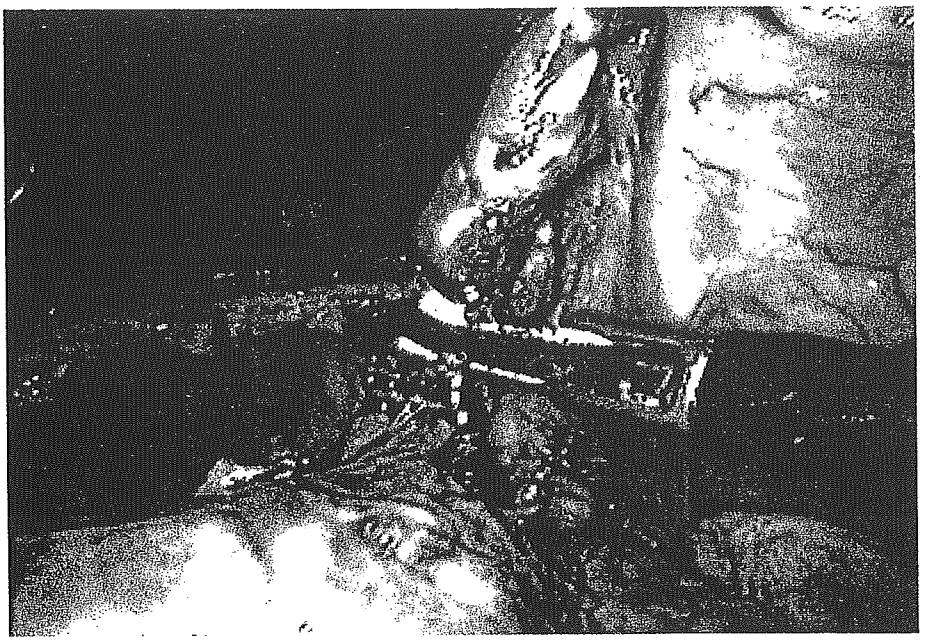


図4

図5

離する（図4）。

6） No. 1, 3 リンパ節郭清

左胃動静脈の切離の後，胃上部後壁を指標にして超音波凝固切開装置を用い，食道胃接合部まで小彎側の脂肪塊を後腹膜腔から剝離していく。次に胃前面と後面からのアプローチにて，超音波凝固切開装置を用いNo. 1，3のリンパ節郭清を行う（図5）。この際，迷走神経も切離しておく。

2. 小開腹創からの操作

上腹部に約5 cmの小開腹をおき，切除予定の幽門側の胃を体外に引き出す。開腹手術と同様に直視下に幽門側胃切除を行った後，Billroth-Ⅰ法による再建を行う。日本内視鏡外科学会（JSES）によるアンケート調査によると，縫合不全や吻合部狭窄など吻合に関する合併症が比較的多い。患者QOLの向上とより安全な吻合をめざして，近年，腹腔鏡下にRoux-en Y吻合などが試みられている。