5. The lesser omentum is opened and the suprapyloric lymph nodes are dissected after the right gastric artery and vein are divided between clips.
6. The stomach is fully mobilized, and the left gastric artery and vein are divided using clips and ligatures (Fig. 6).
7. The left cardiac and superior gastric lymph nodes are dissected down to the distal portion of the stomach (Fig. 7).
8. A 5-cm-long upper midskin incision is made just below the xiphoid, and the mobilized stomach is pulled out through this minilaparotomy wound. The distal two-thirds of the stomach is resected using staplers (Fig. 8).
9. The perigastric lymph nodes are completely dissected along with the distal portion of the stomach.
10. Billroth I gastroduodenostomy is carried out through the minilaparotomy wound, with the same handsewn technique as used for conventional open surgery (Fig. 9).

Other Types of Laparoscopic Gastrectomy

Given the tools available today, laparoscopic proximal and total gastrectomies are still challenging [25–28]. In both these procedures, esophageal anastomosis is performed laparoscopically [26]. Even with the use of a circular stapler, however, this part of the surgery is technically complicated. The totally laparoscopic approach may become easier with the development of improved staplers for transoral application. Hand-assisted laparoscopy, using one of the currently available devices, may simplify the performance of these highly complex procedures. More recently, to preserve the function of the gastric remnant after gastrectomy, some surgeons have performed a laparoscopic pylorus-preserving gastrectomy without injuring vegal nerves such as the pyloric or hepatic branch [10].

Short-Term Outcome

Several case-controlled studies have evaluated the short-term outcome of laparoscopic surgery for early gastric carcinoma. The advantages of laparoscopic gastric resection compared with open gastric resection are summarized in Table 1. Prospective and retrospective analyses by a single institution showed bowel function recovery between 1 and 3 days after laparoscopic gastric resection. In several case-controlled studies, bowel function recovered significantly faster after laparoscopic gastrectomy than after open gastrectomy. In addition, patient quality of life has been assessed by several studies, focusing mainly on postoperative pain and analgesic requirements. In several studies, pain after laparoscopic surgery was also significantly less than that after open surgery [2,5,6].

Other short-term advantages of the laparoscopic procedures were demonstrated by a randomized trial at a single institution, which revealed better postoperative pulmonary function in 14 patients who underwent LADG compared to 14 patients who underwent open distal gastrectomy [29]. Patients after laparoscopic surgery had a significantly faster recovery in forced respiratory volume per second and in forced vital capacity.

Regarding the cost, a case-controlled study showed that LADG is less expensive than conventional open gastrectomy (total hospital charge, ¥1336 $\times$ 10^3 vs. ¥1411 $\times$ 10^3)

TABLE 1. Short-term benefits of laparoscopic gastrectomy compared with open gastrectomy

Clinical course after operation:
Less blood loss
Reduced analgesic request
Earlier first eating
Earlier first flatus
Earlier first walking
Earlier hospital discharge
Lower hospital cost
Better cosmesis
Pulmonary function
Better forced capacity at post operative day (POD) 3
Better forced expiratory volume in 1 at POD 3
Inflammation
Lower peak of number of white blood cells (WBC)
Lower peak of C-reactive protein (CRP)
Lower peak of inter leukin (IL-6)

because both the postoperative recovery period and the hospital stay are shorter (16.1 vs. 20.5 days) [30]. However, Rosin et al. noted problems with LADG, including the complexity of the procedure and long operating time [31].

Follow-Up Evaluation

With regard to operative curability, the surgical margins and the number of dissected lymph nodes in laparoscopic gastrectomy are equivalent to those in conventional open gastrectomy. Table 2 lists several noncomparative or comparative studies of short-term follow-up evaluation of laparoscopic gastrectomy [4,27,29,32–35]. However, the issues regarding the recurrence rates and the long-term survival rate remain unclear. Most retrospective published studies were composed of a small number of patients and showed short-term follow-up. In addition, no long-term results have been recorded after laparoscopic gastrectomy. In the near future, a multicenter randomized controlled trial is needed to confirm the advantages in the long-term outcome of laparoscopic gastric resection for early gastric carcinoma.

Morbidity Related to Laparoscopic Gastric Resection

A survey conducted by the Japan Society for Endoscopic Surgery showed the incidences of intraoperative and postoperative complications to be 2.1% and 4.6% after LWR and 4.2% and 6.5% after IGWR, respectively [36]. The major intraoperative and postoperative complications are bleeding and gastric dysemptying, respectively, for both LWR and IGMR. After LADG, the incidences of intraoperative and postoperative complications are 1.4% and 9.7%, respectively. The major intraoperative complication after LADG is bleeding and the major postoperative complications are gastric dysemptying, anastomotic leakage, and wound infection. Recently, a randomized controlled trial of a small number of cases demonstrated no significant difference in the incidence of complications, such as anastomotic leakage, anastomotic

TABLE 2. Follow-up evaluation of laparoscopic gastrectomy

Authors	Year	Study design	*N*	Candidate	Lymph node disssection	Follow-up (months)	Recurrence (cases)
Azagra et al. [1]	1999	RNC	Lap 13	T2–T3	D1 or D2	Mean, 27.5	2
Hüscher et al. [33]	2000	RNC	Lap 45	T2–T4	D1 or D2 or D3	Mean, 43	1
Ballesta-Lopez et al. [34]	2002	RNC	Lap 25	T1–T2	D1	7–63	0
Kitano et al. [29]	2002	RNC	Lap 116	T1	D1	Mean, 45	0
Tanimura et al. [27]	2003	RNC	Lap 28	T1	D1 or D2	1–36	0
Reyes et al. [4]	2001	RC	Lap 9 Open 12	Stage I–IV	Not described	1–36	0
Kitano et al. [35]	2002	PR	Lap 14 Open 14	T1	D1	Mean, 21.5	0

RNC, retrospective noncomparative study; RC, retrospective comparative study; PR, prospective randomized controlled study; Lap, laparoscopic gastrectomy; Open, open gastrectomy

stenosis, bleeding, and wound infection, between an LADG group and a conventional open gastrectomy group [29]. However, laparoscopic gastric resection for gastric carcinoma is still under development. Under laparoscopic surgery, some adverse events occur that are technically associated with laparoscopic gastrectomy.

Bleeding

Bleeding related to lymph node dissection is the most frequent complication during laparoscopic gastrectomy. It is important to recognize the anatomy as seen in a limited, two-dimensional monitor and to maintain a perspective that allows the prevention of accidental bleeding.

Injury of the Gastrointestinal Tract

When the walls of the stomach, transverse colon, or duodenum are strongly grasped by forceps to extend them, they can be accidentally injured. If these injuries happen, they should be repaired carefully by an intraabdominal suturing technique or automatic suturing.

Injury of Solid Organs

When the lymph node is dissected superior to the pancreas, parenchyma of the pancreas can be injured accidentally by forceps or by an ultrasonically activated device. The liver and spleen also can be injured when they are strongly retracted. All procedures should be done gently and carefully under laparoscopic surgery because of the limited operative view and the mobility of each instrument.

Port Site Metastasis

The issues of port site metastasis are still unresolved. Therefore, a understanding of physiology and the development of correct measures are needed to prevent it. Although recent papers in a clinical setting have demonstrated that laparoscopic colectomy in patients with advanced colorectal cancer has a long-term survival rate equivalent to that of open surgery and does not increase port site metastases [37–39], it is dangerous to apply these results for colorectal cancer to advanced gastric carcinoma. The few reported cases regarding port site metastasis in gastric carcinoma were all related to advanced tumors or diffuse carcinomatosis [33]. The presence of serosal penetration may be associated with this phenomenon.

Conclusion

Laparoscopic surgery for gastric carcinoma has been shown to be potentially superior to traditional laparotomy with regard to short-term benefits. The technique seems safe and capable of fulfilling oncological criteria for cancer surgery. However, questions regarding recurrence rates and long-term survival have not yet been satisfactorily answered. Further follow-up and a review of large, multicenter randomized trials are needed before widespread acceptance of the technique can be recommended. Finally, surgeons with sufficient expertise and ongoing peer-reviewed data collection may currently offer this therapy to appropriately selected patients.

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Color Plates

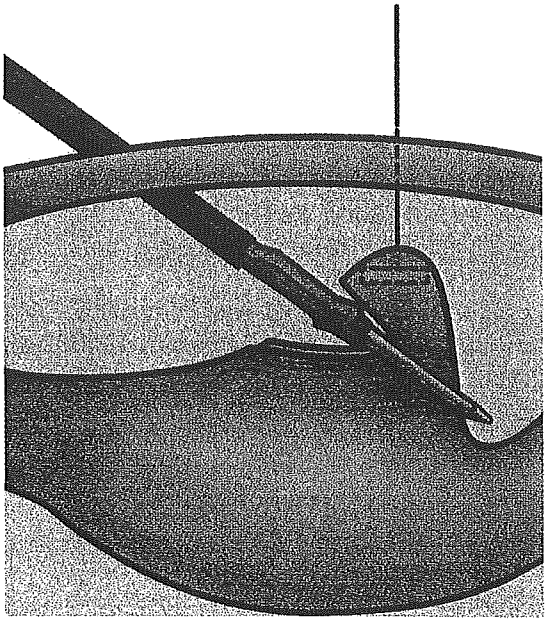


FIG. 1. Local wedge resection (LWR) by the lesion-lifting method

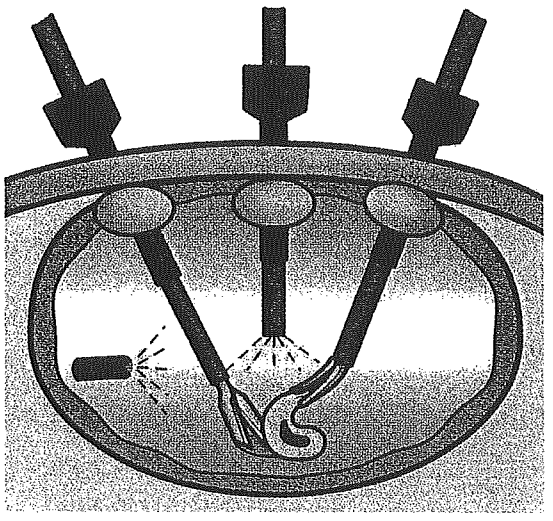


FIG. 2. Intragastric mucosal resection (IGMR)

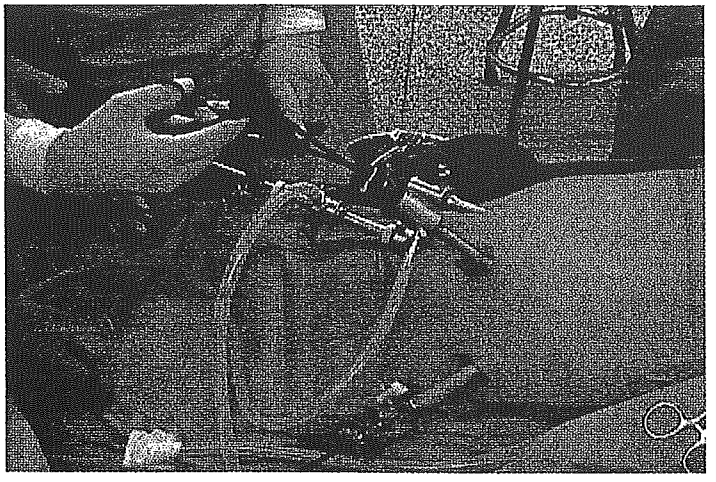


FIG. 3. Placement of four cannulas

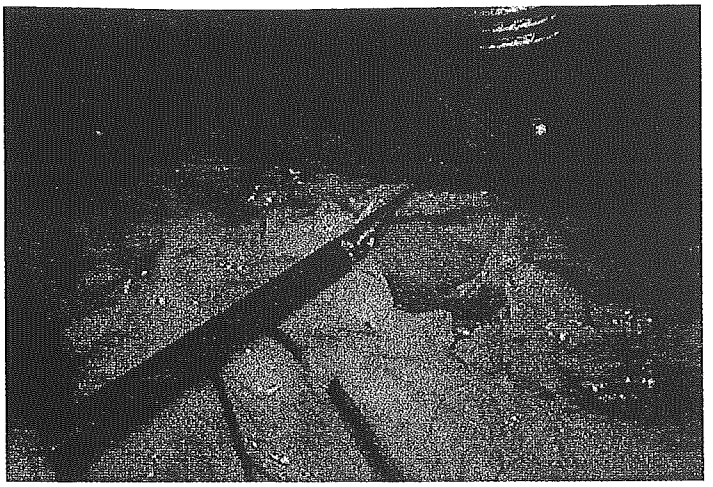


FIG. 4. Dissection of the greater omentum and gastrocolic ligament outside the epigastric arcade

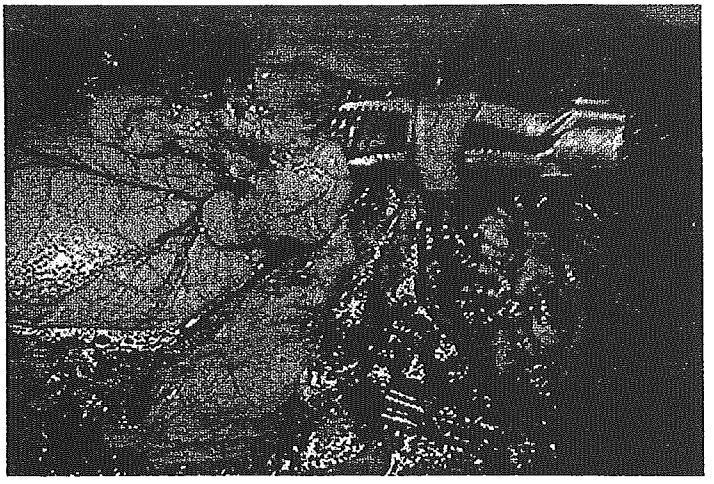


FIG. 5. Cutting the right gastroepiploic vessels

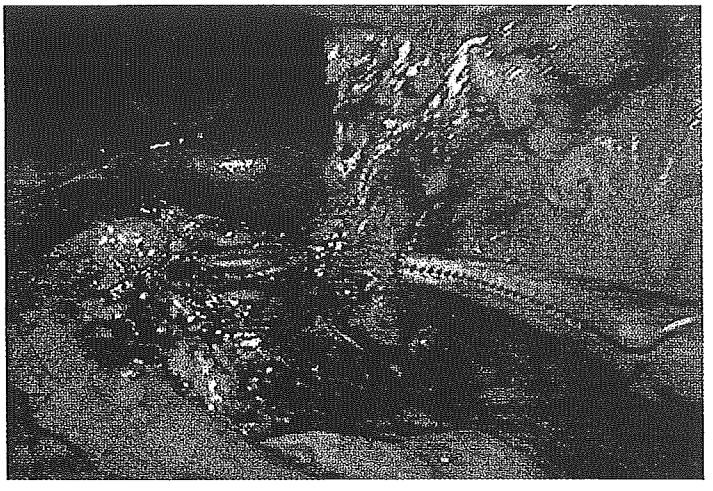


FIG. 6. Cutting the left gastric vessels

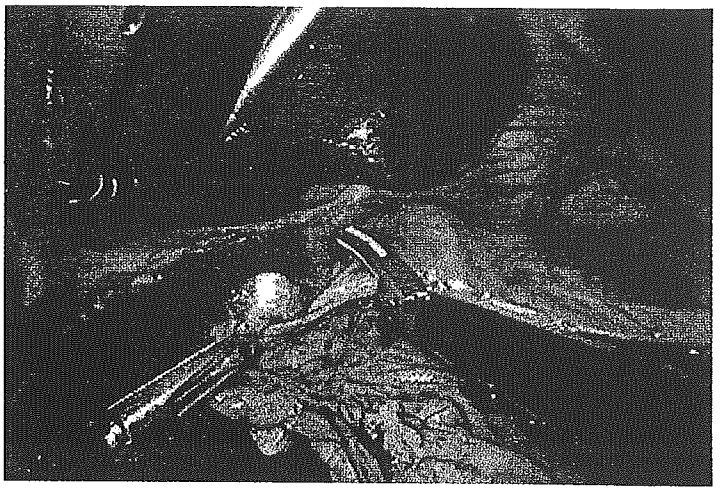


FIG. 7. Dissection of the left cardiac and superior gastric lymph nodes

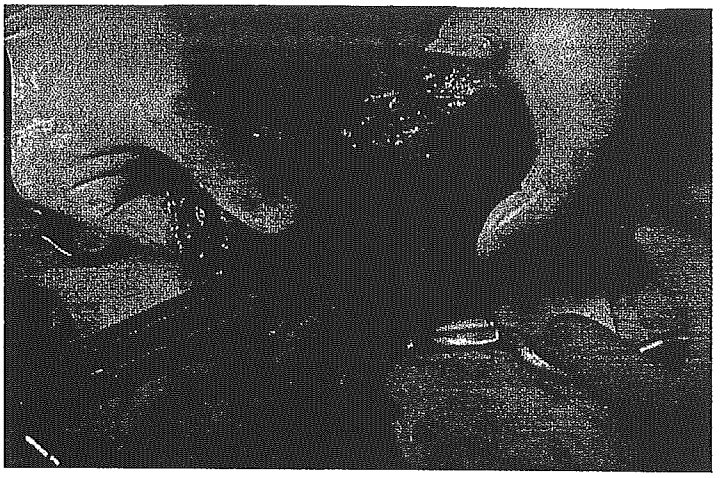


FIG. 8. Resection of the distal two-thirds of the stomach through a minilaparotomy wound

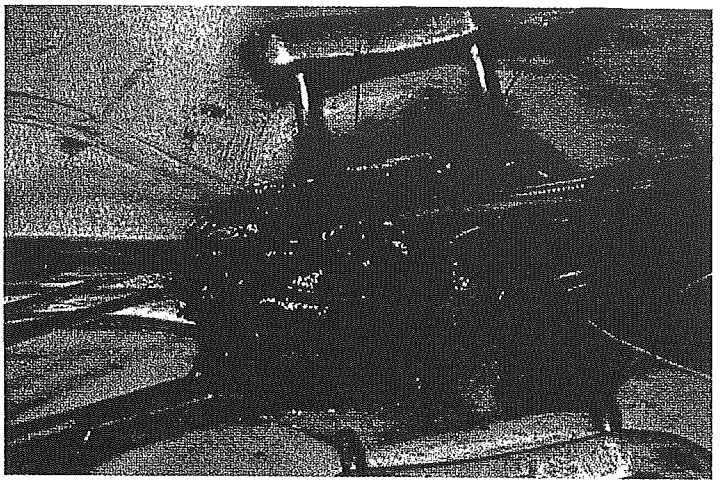


FIG. 9. Anastomosis by Billroth I method

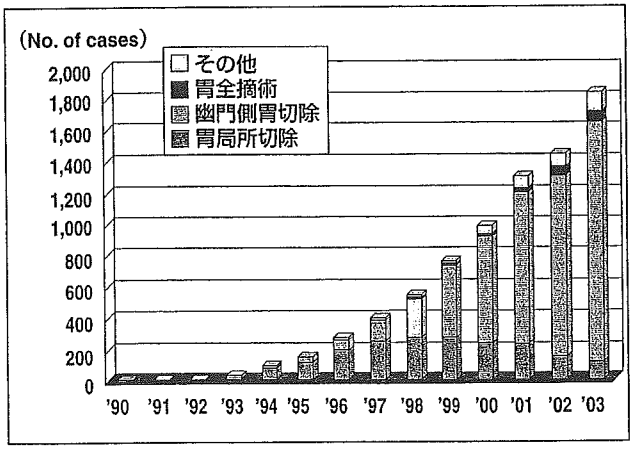
1-1　腹腔鏡下胃切除術の現状

要点

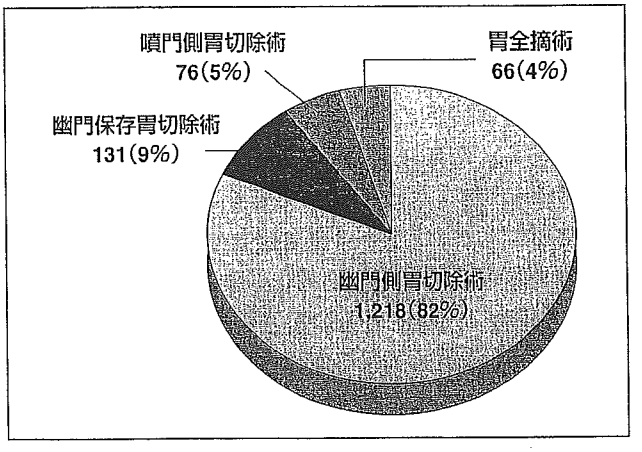
1. 胃癌に対する腹腔鏡下胃切除術の中で特に幽門側胃切除術の増加が目覚ましく，腹腔鏡下胃切除術の4/5を占めている．
2. その主な適応は，EMRの適応とならない早期胃癌を対象としており，その際のリンパ節郭清はD1+αとD1+βが選択されている．
3. 早期胃癌を対象として開発された腹腔鏡下胃切除術は，T2N0，T2N1の進行癌にまで適応拡大が試みられている．
4. 本術式の術中偶発症と術後合併症の発生頻度は2%と12%であり，術中偶発症としては出血と他臓器損傷が，術後合併症としては吻合部に関するものが多い．
5. 早期胃癌に対する本術式の術後無再発生存率は，従来の開腹手術と同等であった．進行胃癌に対する本術式の検討が今後の課題である．

腹腔鏡下胃切除術の動向(図1-1，2)

1991年，早期胃癌に対する腹腔鏡補助下幽門側胃切除術(LADG)が最初に行われて以来[1]，腹腔鏡下手術の特徴である低侵襲性と術後患者QOLの向上を目的として新しい手技上の工夫と症例数の大幅な増加がみられている．**図1-1**に日本内視鏡外科学会の第7回アンケート調査結果を示す[2]．LADGは，年々増加し，これまでに総計5,200例が行われてきた．2003年の1年間には1,800例(腹腔鏡下胃切除術の83%を占める)が施行されている．厚生労働省北野班によるアンケート調査結果[3]によると，**図1-2**のように，幽門側胃切除術の他，幽門保存胃切除術(9%)，噴門側胃切除術(5%)，胃全摘術(4%)などの腹腔鏡下手術が行われている．



[図1-1]　胃癌に対する腹腔鏡下手術
(第7回アンケート調査，2004，JSES，文献2)

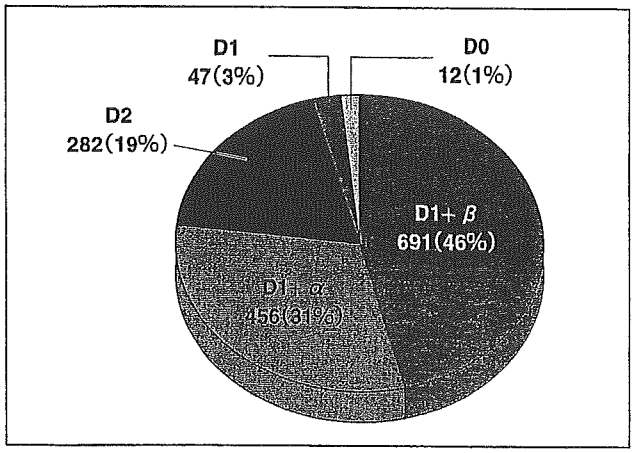


[図1-2]　早期胃癌に対する腹腔鏡下胃切除術(局所切除を除く)
局所切除を除いた1,491例の術式別内訳である．幽門側胃切除術82%の他，幽門保存胃切除術，噴門側胃切除術，胃全摘出術が行われた．(厚生労働省北野班第4回アンケート調査)

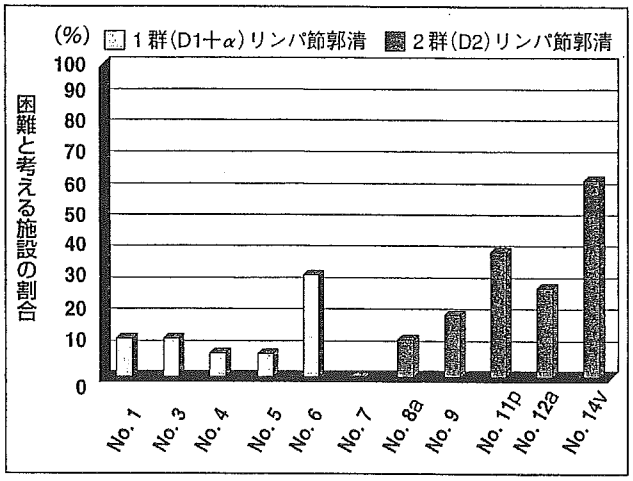
腹腔鏡下リンパ節郭清(図1-3，4)

本手術は，内視鏡的粘膜切除(EMR)の適応を越える早期胃癌に対して，D1+ αのリンパ節郭清を行う手術として誕生した．近年，手術手技の向上と新しい機器の開発により腹腔鏡下手術によるリンパ節郭清範囲が広がっている．**図1-3**は，厚生労働省北野班によるアンケート調査結果である．早期胃癌に対して最も多く施行されている腹腔鏡下リンパ節郭清範囲は，D1+ βであった．さらに現在，T2N0，T2N1の進行胃癌に対しても腹腔鏡下胃切除術を試みている施設もあり，リンパ節郭清範囲がD2へと拡大されてきた．

一方，開腹手術においてリンパ節郭清範囲の拡大とともに術中偶発症や術後合併症の増加が報告されている．腹腔鏡下手術においても同様なことが懸念されている．厚生労働省北野班では，安全な腹腔鏡下リンパ節郭清を心がけるため，どのリンパ節郭清が手技的に難しいかをアンケート調査した．その結果，**図1-4**のように，D1+ αのリンパ節郭清ではNo.6リンパ節郭清が，またD2ではNo.11p，12a，14vリンパ節郭清が難しいと考えている施設が多く，これらのリンパ節郭清の際には，十分注意し安全な手技を行う必要がある．



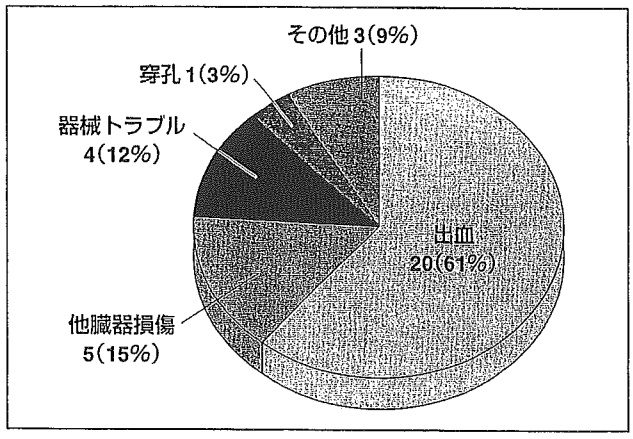
[図1-3] リンパ節郭清
約60%がm癌で，77%にD1+ α，βが施行されている．(厚生労働省北野班第4回アンケート調査)



[図1-4] 腹腔鏡下リンパ節郭清手技の難易度
2群リンパ節郭清に関して，No.6，11p，14v，12aなどの郭清手技が難しいと考えている施設が多く，このような手技を確立する必要があると思われる．(厚生労働省北野班第4回アンケート調査)

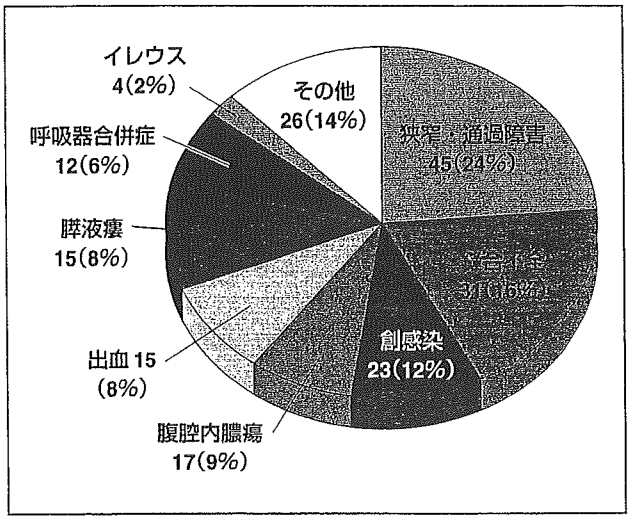
術中偶発症と術後合併症(図1-5，6)

術中偶発症は，手技に起因するものがその大半を占めている．それゆえ，術中偶発症の発生頻度とその内訳を十分に理解しておく必要がある．**図1-5**に厚生労働省北野班によるアンケート調査結果を示す．早期胃癌に対する腹腔鏡下胃切除術における術中偶発症の発生頻度は2%であり，出血と他臓器損傷によるものが多かった．出血は，左胃動静脈と短胃静脈，さらには脾損傷による出血が多いことが示された．鉗子操作や超音波凝固切開装置の使用に十分習熟して，安全な操作を心がけたいものである．



[図1-5] 術中偶発症
発生率は2%で出血が多い．(厚生労働省北野班第4回アンケート調査)

一方，**図1-6**に術後合併症に関するアンケート調査結果を示した．術後合併症の発生率は12%であり，その約40%が吻合部に関するものであった．縫合不全と吻合部狭窄を生じた症例の約半数が手縫いであり，残り半数が器械吻合であった．縫合不全を生じた器械吻合の大半は，自動吻合器(circular stapler)を用いたものであり，使用に際しては十分な注意が必要である．また創感染は，本術式の特徴である低侵襲性を損なうこととなるため，創部の保護や感染予防に十分気をつける必要がある．



[図1-6] 術後合併症
発生率は12%で吻合部のトラブルが多い．(厚生労働省北野班第4回アンケート調査)

無再発生存率

厚生労働省北野班によるアンケート調査結果において早期胃癌に対する腹腔鏡下胃切除術の5年無再発生存率は約99%であり，開腹手術と同等であると思われる．一方，進行胃癌に対するその評価は，今後の症例の蓄積を待ちたい。

[北野正剛]

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3) 厚生労働省がん研究助成金「がんにおける体腔鏡手術の適応拡大に関する研究」第4回アンケート調査結果報告．厚生労働省がん研究助成金北野班(主任研究者：北野正剛)．2004, 9

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SURGICAL ENDOSCOPY
and Other Interventional Techniques

Morphological changes in hepatic vascular endothelium after carbon dioxide pneumoperitoneum in a murine model

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Abstract

Background: Liver metastasis is an important prognostic factor in advanced colorectal cancer. Several studies have demonstrated that carbon dioxide (CO_2) pneumoperitonem enhances liver metastasis in an animal model. In the present study, we used scanning electron microscopy (SEM) to investigate morphological changes in hepatic vascular endothelium after CO_2 pneumoperitoneum in a murine model.

Methods: Thirty-three male BALB/c mice were randomized to undergo pneumoperitoneum (CO_2, air, or helium), open laparotomy, and anesthesia alone. After each procedure, the animals' livers were excised at days 0, 1, and 3 and examined by SEM.

Results: In the CO_2 pneumoperitoneum group, we observed rough surface and derangement of the hepatic vascular endothelial cells and intercellular clefts on day 1. In the other groups, no major morphologic changes were observed at any time.

Conclusions: Hepatic vascular endothelium changes after CO_2 pneumoperitoneum. Such characteristic changes may play an important role in establishing liver metastasis after CO_2 pneumoperitoneum.

Key words: Laparoscopic surgery — Pneumoperitoneum — Carbon dioxide — Murine model — Scanning electron microscopy — Colorectal cancer — Liver metastasis

Laparoscopic surgery yields favorable short-term clinical outcomes in the management of colorectal malignancies. As a less invasive alternative to open surgery, it has been shown to be technically feasible and to improve patient comfort. There have been few reports, however, on long-term outcomes.

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Liver metastasis is the most important prognostic factor in advanced colorectal cancer. Therefore, the effects of pneumoperitoneum on liver metastasis of colorectal cancer have been a matter of cancer. Several experimental studies have shown that carbon dioxide (CO_2) pneumoperitoneum enhances liver metastasis [4–7]. Carbon dioxide pneumoperitoneum causes a decrease in portal blood flow [13, 18, 19] and provides favorable conditions for the adherence of free tumor cells, which can then spread into the portal system, to the hepatic vascular endothelium. However, it is uncertain whether morphological changes occur in the hepatic vascular endothelium after surgical procedures such as the CO_2 pneumoperitoneum or open laparotomy.

In the present study, we used a murine pneumoperitoneum model to investigate morphological changes in hepatic vascular endothelium by scanning electron microscopy (SEM).

Materials and methods

Animals

Thirty-three male BALB/c mice weighting 20–24 g and aged 6–8 weeks were used in this study. All animals were kept under standard laboratory conditions (temperature, 20–24°C; relative humidity, 50–60%; 12 h light/dark cycles) and given a standard laboratory diet with free access to water and food. All experiments were performed under the guidelines for animal experimentation of the Oita University Faculty of Medicine.

Procedures

All surgical procedures were performed under general anesthesia induced by diethyl ether inhalation. Thirty-three BALB/c mice were divided into three operative groups; pneumoperitoneum, laparotomy, and anesthesia only (control).

In the pneumoperitoneum group, nine mice underwent CO_2 pneumoperitoneum at 8–10 mmHg for 60 min and were killed after either 0 h (n = 3), 24 h (n = 3), or 72 h (n = 3). In addition, six mice received an air or helium (n = 3 each) pneumoperitoneum at 8–10 mmHg for 60 min and were killed after 24 h. The procedure for

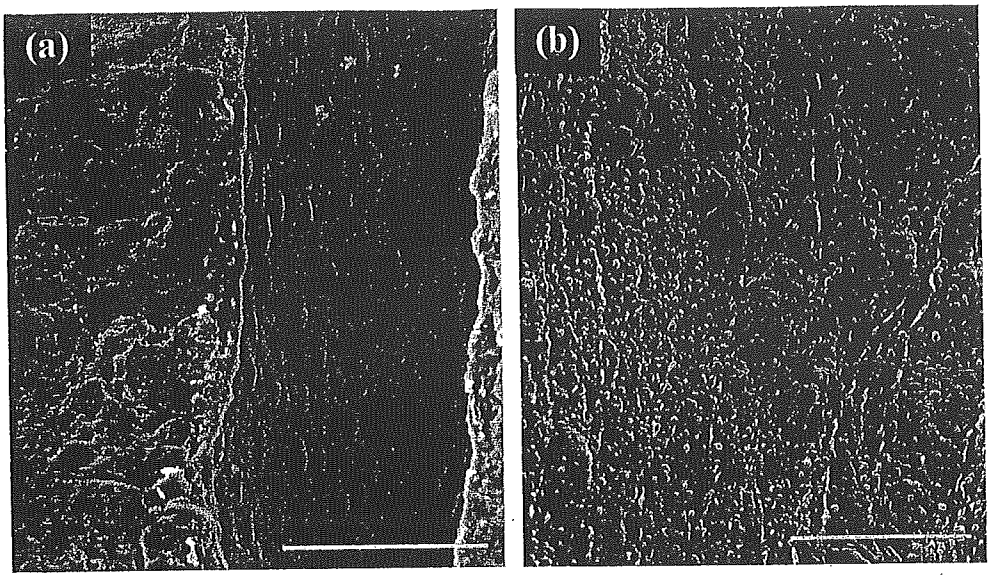

Fig. 1. Hepatic vascular endothelium of untreated mice. **a** Original magnification, ×500. The bar represents 60 μm. **b** Original magnification, ×2,000. The bar represents 15 μm.

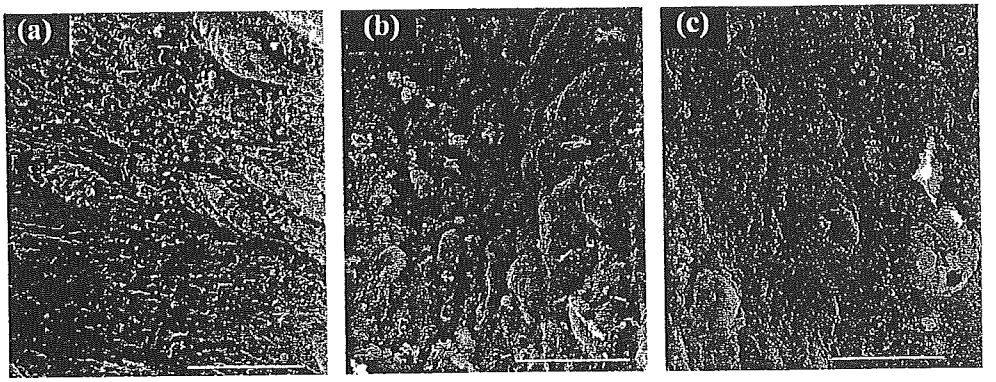

Fig. 2. In the CO_2 pneumoperitoneum group, there were marked changes in the hepatic vascular endothelium. Dilatation of intercellular clefts, irregular arrangement of endothelial cells, and a rough surface were observed. Original magnification, ×2,000. The bar represents 15 μm. **a** Immediately after CO_2 pneumoperitoneum. **b** Day 1. **c** Day 3.

establishing the pneumoperitoneum has been described previously [16]. A 22-gauge intravenous cannula was inserted into the left lower quadrant and used as an insufflation needle. A 20-gauge intravenous cannula was inserted into the right lower quadrant and used to measure intraperitoneal pressure. A disposable syringe was used to inject the gas. A syringe pump was used to maintain 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 = 9), a 3-cm abdominal midline incision was made, and the laparotomy conditions were maintained for 60 min. The mice were killled after either 0 h (n = 3), 24 h (n = 3), or 72 h (n = 3).

The control group (n = 9) underwent only diethyl ether anesthesia for 60 min. The mice were killed after either 0 h (n = 3), 24 h (n = 3), or 72 h (n = 3).

After each procedure, the left lobe of the murine liver was excised, and four samples from each liver were prepared for examination with an SEM. These samples were put into fixative solution composed of 2% formaldehyde and 2.5% glutaraldehyde in 0.05 M cacodylate buffer solution. They were then placed into 1% osmium tetroxide for 60 min, dehydrated stepwise in alcohol, and dried by mens of a critical points apparatus. The dried specimens were mounted on aluminium stubs, spatter-coated with gold, and examined with an SEM (Hitachi S800, Ibaragi, Japan). Photographs of the five areas selected at random in each sample were analyzed.

None of the animals died at any time during this experiment.

Analysis

Following the same procedure used by Suematsu et al. [17], the photographs were evaluated by five independent observers (one histologist, one pathologist, and three surgeons) who were not informed of the procedures used to quantify the results. The following characteristics of the hepatic vascular endothelium were observed: (a) dilatation of intercellular clefts, (b) derangement of the endothelial cells, and (c) a rough surface. We then compared these characteristics with those of normal hepatic vascular endothelium of untreated mice and graded the changes as none or slight (−), moderate (+), or marked (+ +). If over half of the observers were in agreement, the results were adopted. In cases where the observers disagreed about the results, the lower grade was adopted.

Results

Figure 1 shows the normal hepatic vascular endothelium of untreated mice. Normal liver endothelium is characterized by a smooth surface, a regular arrangement of the endothelial cells that corresponds with the direction of the blood flow, and no intercellular clefts. In the CO_2 pneumoperitoneum group (Fig. 2), we observed both derangement of the hepatic vascular endothelial cells and intercellular clefts on day 1. These changes were recognized immediately after creation of the CO_2 pneumoperitoneum and persisted 3 days. However, in the air pneumoperitoneum group, the changes were not as marked on day 1 (Fig. 3a). Also, on day 1 after helium pneumoperitoneum, the changes were unremarkable (Fig. 3b). There were also no remarkable changes at any time in the control group or the laparotomy group

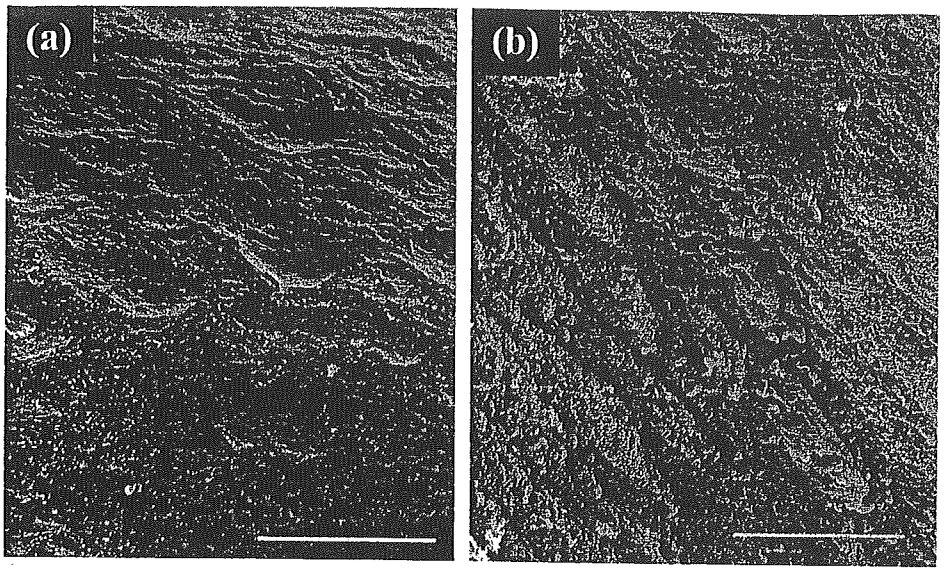

Fig. 3. In both the air (a) and helium (b) pneumoperitoneum groups, changes to the hepatic vascular endothelium were slight as compared with the CO_2 pneumoperitoneum group on day 1. Original magnification, ×2,000. The bar represents 15 μm.

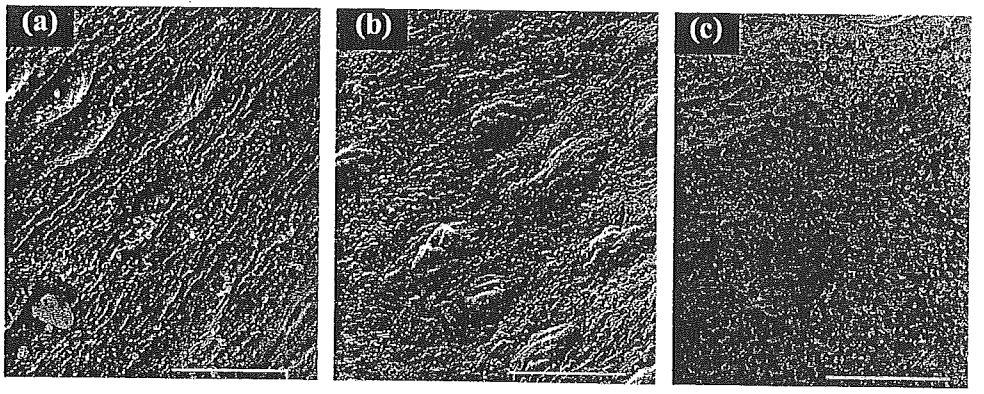

Fig. 4. In the control group, there were only minimal changes to the hepatic vascular endothelium. Original magnification, ×2,000. **a** Immediately after ether anesthesia. **b** Day 1. **c** Day 3. The bar represents 15 μm.

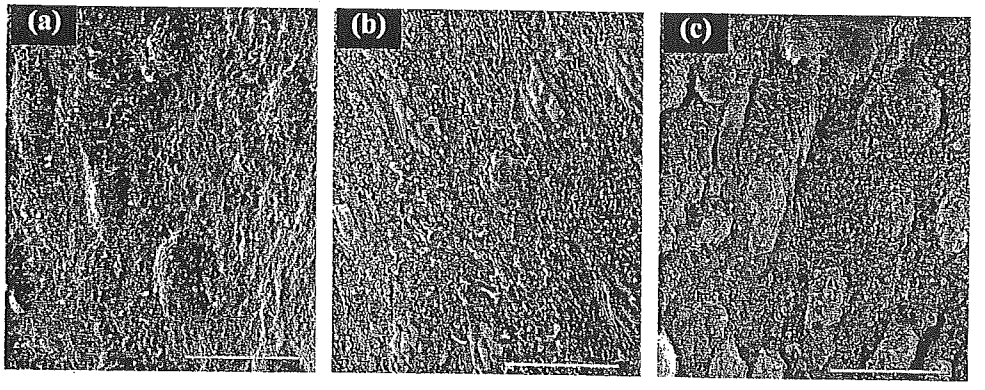

Fig. 5. In the laparotomy group, there were only minimal changes to the hepatic vascular endothelium. Original magnification, ×2,000. **a** Immediately after laparotomy. **b** Day 1. **c** Day 3. The bar represents 15 μm.

(Figs. 4 and 5). In the laparotomy group, only the rough surface of endothelium was observed on day 3, but this change was slight as compared with the CO_2 pneumoperitoneum group.

Table 1 summarizes the morphological changes in each group. There were no wide disparities among the five observers in grading the results.

Discussion

Laparoscopic surgery has been adopted for colorectal cancer because it is less invasive and yields a better cosmetic result. However, the effects of the pneumoperitoneum on liver metastasis, which is the most important prognostic factor for colorectal cancer, remain unclear. In the present study, we used SEM to investigated the morphologic changes to hepatic vascular endothelial cells that occur after CO_2 pneumoperitoneum. Other studies have used SEM to investigate morphological changes to the peritoneum after CO_2 pneumoperitoneum [17, 20], but this is the first study to clarify changes to the hepatic vascular endotheliem after CO_2 pneumoperitoneum.

The first step in liver metastasis is the adherence of tumor cells to the hepatic vascular endothelium. Thus,

Table 1. Summary of morphological changes of hepatic vascular endothelium after carbon dioxide (CO_2), helium, or air pneumoperitoneum, laparotomy, or anesthesia alone

	Dilatation of intercellular clefts	Irregular arrangement of endothelial cells	Rough surface
Immediately after each procedure			
CO_2	–	+	–
Laparotomy	–	–	–
Anesthesia	–	–	–
24 h after each procedure			
CO_2	++	++	++
Air	–	–	+
Helium	–	–	+
Laparotomy	–	–	–
Anesthesia	–	–	–
72 h after each procedure			
CO_2	+	+	+
Laparotomy	–	–	+
Anesthesia	–	–	–

–, none or slight; +, moderate; ++, marked

injury to the hepatic vascular endothelium may be associated with an increase in the incidence of liver metastasis. In hepatic ischemia-reperfusion injury, the damage to the ischemic lobe creates a favorable condition for liver metastasis or intrahepatic tumor growth [2], and the expression of adhesion molecules promotes the establishment of liver metastasis.

Several studies have previously shown that the intraabdominal insufflation of CO_2 causes a marked and rapid decrease (35% to 84%) in portal blood flow [8, 12, 14]. This reduction correlates with the degree of intraabdominal pressure, and may be caused by either mechanical compression of the thin-walled portal vein or hypercapnia-induced vasoconstriction; by contrast, the hepatic arterial flow appears to be less compromised. In this study, intraabdominal pressure was kept at 8–10 mmHg after insufflation in the pneumoperitoneum group. This high level of intraabdominal pressure must influence portal blood flow, and it may serve to induce hepatic ischemia after creation of the pneumoperitoneum.

In the CO_2 pneumoperitoneum group, we observed distinct morphological changes to the hepatic vascular endothelium, including (a) dilatation of intercellular clefts, (b) irregular arrangement of the endothelial cells, and (c) a rough surface. On day 1 after CO_2 pneumoperitoneum, these changes were remarkable. However, on day 1 after air and helium pneumoperitoneum, the changes to the hepatic vascular endothelium were comparatively slight. Our results suggest that these morphological changes are caused not only by the reduction in portal blood flow induced by intraabdominal high pressure but also by the CO_2 itself.

Shuto et al. [15] have shown that metabolic acidosis occurs after both helium and CO_2 pneumoperitoneum, but hypercapnia occurs only after CO_2 pneumoperitoneum. Furthermore, several studies have shown that whereas helium pneumoperitoneum does not cause either hypercapnia or acidic changes, CO_2 pneumoperitoneum induces both hypercapnia and acidosis[1, 3, 9–11]. Therefore, morphological changes to the hepatic vascular endothelium may be a result of a combination of CO_2 absorption and the hepatic ischemia induced by the CO_2 pneumoperitoneum.

In conclusion, morphological changes to the hepatic vascular endothelium occur after CO_2 pneumoperitoneum. Clinical studies are needed to investigate whether these changes are associated with the enhancement of liver metastasis after laparoscopic colorectal surgery.

Acknowledgment. This study was supported in part by a Grant-in-Aid for Scientific Research (no. 15390401) from the Japanese Ministry of Education, Science, and Culture. We also thank Tatsuo Shimada, Department of Fundamental Nursing, Oita University Faculty of Medicine, for his support of our work.

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Clinical Trial Note

Randomized Controlled Trial to Evaluate Laparoscopic Surgery for Colorectal Cancer: Japan Clinical Oncology Group Study JCOG 0404

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[1]Department of Gastroenterological Surgery, Oita University Faculty of Medicine, Oita, [2]Medical Oncology Division, [4]Colorectal Surgery Division, National Cancer Center Hospital and [3]Statistics and Cancer Control Division, National Cancer Center Research Center for Cancer Prevention and Screening, Tokyo, Japan

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A randomized controlled trial was started in Japan to evaluate whether laparoscopic surgery is the optimal treatment for colorectal cancer. Patients with T3 or deeper carcinoma in the colorectum without transverse and descending colons are pre-operatively randomized to either open or laparoscopic colorectal resection. Surgeons in 24 specialized institutions will recruit 818 patients. The primary end-point is overall survival. Secondary end-points are relapse-free survival, short-term clinical outcome, adverse events, the proportion of conversion from laparoscopic surgery to open surgery, and the proportion of completion of laparoscopic surgery.

Key words: colorectal cancer – laparoscopic surgery – randomized controlled trial

INTRODUCTION

The benefits of laparoscopic surgery (LAP) in comparison with open surgery (OPEN) have been suggested with respect to decreased morbidity, decreased pain, faster recovery and shorter hospital stay (1–4). However, the long-term survival of LAP for colorectal cancer is still unclear, especially for advanced colorectal cancer requiring extended lymphadenectomy. Thus, we designed a study which investigates whether LAP is suitable for advanced colorectal cancer with respect to survival and post-operative morbidity. The Clinical Trial Review Committee of the Japan Clinical Oncology Group (JCOG) approved the protocol in September 2004, and the study was activated in October 2004.

PROTOCOL DIGEST OF THE JCOG 0404

PURPOSE

To evaluate LAP in comparison with OPEN for T3 and T4 colorectal cancer.

Seigo Kitano, study chair; Masafumi Inomata, study coordinator; Akihiro Sato, protocol coordinator; Kenichi Yoshimura, study statistician; Yoshihiro Moriya, group chair
For reprints and all correspondence: Seigo Kitano, Department of Gastroenterological Surgery, Oita University Faculty of Medicine, 1-1 Hasama-machi, Oita, 879-5593, Japan. E-mail: colonrct@med.oita-u.ac.jp

STUDY SETTING

A multi-institutional (24 specialized centers), randomized controlled trial.

RESOURCES

Health and Labour Sciences Research Grants for Clinical Research for Evidenced Based Medicine, Clinical Cancer Research and Grants-in-Aid for Cancer Research (14S-4, 17S-5), from the Ministry of Health, Labour and Welfare, Japan.

END-POINTS

The primary end-point is overall survival. Secondary end-points are relapse-free survival, short-term clinical outcomes, adverse events, the proportion of conversion from LAP to OPEN and the proportion of completion of LAP. All LAP cases which require skin incision >8 cm are counted as a conversion to OPEN, except for those in which retrieval of the resected specimen alone requires this length of incision. The completion of LAP is defined as completion of the curative operation without conversion to OPEN. The short-term clinical outcomes are proportion of use of analgesics, duration from operation to flatus, highest body temperature during hospitalization and highest body temperature during the 3 days after the operation.

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Eligibility Criteria

Tumors are staged according to the TNM classification system.

Inclusion criteria. For inclusion in the study, patients must fulfill the following requirements pre-operatively: (i) histologically proven colorectal carcinoma; (ii) tumor located in the cecum, ascending colon, sigmoid colon or rectosigmoid colon; (iii) T3 or deeper lesion without involvement of other organs; (iv) without multiple lesions other than carcinoma *in situ*; (v) cancer classified as N0–2 and M0, according to the TNM classification system; (vi) tumor size ≤8 cm; (vii) no bowel obstruction; (viii) age ≥20 and <75 years; (ix) sufficient organ function; (x) no history of gastrointestinal surgery; (xi) no history of chemotherapy or radiotherapy; and (xii) provide written informed consent.

Exclusion criteria. Exclusion criteria are as follows: (i) synchronous or metachronous (within 5 years) malignancy other than carcinoma *in situ*; (ii) severe pulmonary emphysema, interstitial pneumonitis or ischemic heart disease; (iii) pregnant or lactating women; (iv) severe mental disease; and (v) continuous systemic steroid therapy.

Randomization

By telephone or fax to the JCOG Data Center after confirmation of the inclusion/exclusion criteria, the patients are randomized by the minimization method of balancing the arm according to the location of tumor and institution.

Quality Control of Surgery

To control the quality of the operation, we limit the operator to accredited surgeons and perform central review of the surgical procedure by photograph in all patients and by videotape in arbitrarily selected patients in both the LAP and OPEN arms. All operations are done or directly supervised by certified surgeons. Surgeons who have experience of at least 30 cases of open surgery in the OPEN arm, and experience of at least 30 case of both open and laparoscopic surgeries in the LAP arm are certified by the study chair.

Treatment Method

In both arms, resection of the colon or rectum with D3 lymphadenectomy is performed according to the Japanese Classification of Colorectal Carcinoma (5). In the LAP arm, pneumoperitoneal and intracorporeal approaches are used to explore the abdomen, mobilize the colon, identify critical structures and ligate the vascular pedicle. Mobilization of the colon and identification of critical structures are performed by the pneumoperitoneal approach only. Resection of the colon, ligation of the vascular pedicle and reconstruction are performed by the pneumoperitoneal approach or the intracorporeal approach via a small incision (≤8 cm). Hand-assisted laparoscopic surgery is permitted, but sliding window and moving window methods are not permitted.

Additional Treatment

In the case of pathological stage III colorectal carcinoma, three cycles of adjuvant chemotherapy with fluorouracil (500 mg/m^2 by bolus infusion on days 1, 8, 15, 22, 39 and 36) and l-leucovorin (250 mg/m^2 by 2 h drip infusion on days 1, 8, 15, 22, 39 and 36) are administered.

Follow-up

Patients are observed by their surgeon every 4 months for the first 2 years and then every 6 months for 3 years after operation. Blood tests, abdominal computed tomography and plain chest X-ray are carried out at each visit.

Study Design and Statistical Method

This trial is designed to evaluate the non-inferiority of LAP to standard OPEN in terms of overall survival. If the overall survival is equivalent, LAP will be the preferred treatment. The null hypothesis to be tested is that the hazard ratio for the primary end-point with the LAP technique, as compared with the OPEN technique, was 1.366. The planned sample size is 818, 409 cases per arm, with 5 years of follow-up after 3 years of accrual. This provides 80% power to reject the null hypothesis when the survival is equivalent. This calculation assumed that there was a 5-year survival of 75% among patients treated with the OPEN technique.

Interim Analysis and Monitoring

Interim analysis is planned to take place twice, taking multiplicity into account by the Lan-Demets method with O'Brien and Fleming type boundaries. The Data and Safety Monitoring Committee (DSMC) of the JCOG will independently review the interim analysis report and consider stopping the trial early. In-house interim monitoring will be performed by the Data Center to ensure data submission and study progress. The monitoring reports will be submitted to and reviewed by the CCSG every 6 months.

Participating Institutions (from North to South)

Jichi Medical School Omiya Medical Center, National Cancer Center Hospital East, Juntendo University Urayasu Hospital, Toho University School of Medicine Sakura Hospital, National Cancer Center Hospital, Kyorin University School of Medicine, Keio University Hospital, Tokyo Medical and Dental University, Toranomon Hospital, Toho University School of Medicine Ohashi Hospital, Kitasato University East Hospital, Teikyo University school of Medicine Mizonokuchi Hospital, Ishikawa Prefectural Central Hospital, Showa University Northern Yokohama Hospital, Nagano Municipal Hospital, Shizuoka Cancer Center, Fujita Health University, Osaka University Graduate School of Medicine Faculty of Medicine, Osaka City General Hospital, Osaka Medical College, Hiroshima University

Faculty of Medicine, Shikoku Cancer Center, Kurume University School of Medicine, Oita University Faculty of Medicine.

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