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and Other Interventional Techniques

Current status of laparoscopic gastrectomy for cancer in Japan

S. Kitano, N. Shiraishi

Department of Surgery I, Oita University Faculty of Medicine, 1-1 Idaigaoka, Hasama-machi Oita 879-5593, Japan

Abstract. Because of the increased incidence of early gastric cancer in Japan, minimally invasive laparoscopic approaches to gastric malignancies have been under development since 1991. Laparoscopic local resection of the stomach, i.e., laparoscopic wedge resection (LWR) and intragastric mucosal resection (IGMR), is used to treat mucosal cancer without lymph node metastasis. Laparoscopy-assisted distal gastrectomy (LADG) is used to treat early gastric cancer with risk factors for regional lymph node metastasis. A survey conducted by the Japan Society for Endoscopic Surgery showed that 1428 LWRs, 260 IGMRs, and 2600 LADGs were performed between 1991 and 2001 in departments of endoscopic surgery in Japan. Laparoscopic gastrectomy for gastric cancer is still under development in Japan. According to short-term results reported by a small group of surgeons, laparoscopic approaches to gastric cancer provide for minimal invasion, early recovery, and decreased morbidity and mortality. If the advantages can be confirmed in one or more multicenter randomized control studies of the long-term outcome of patients undergoing laparoscopic gastrectomy for gastric cancer, the procedure should come into wide acceptance and use.

Key words: Early gastric cancer — Laparoscopic wedge resection — Intragastric mucosal resection — Laparoscopy-assisted distal gastrectomy

The incidence of gastric cancer is high in Japan, and cases are managed routinely by surgery with systemic lymph node dissection. Detection of early gastric cancer has increased because of the development of diagnostic techniques such as endoscopy, biopsy, and endoscopic ultrasonography [17]. Because of the high incidence of early gastric cancer, minimal invasiveness is a consideration, and several new surgical procedures with minimal invasiveness have been developed. These include endoscopic mucosal resection (EMR) [20], laparoscopic surgery [7], and pylorus-preserving gastrectomy [22].

Correspondence to: S. Kitano

After the first laparoscopy-assisted distal gastrectomy (LADG) for early gastric cancer was performed in 1991 [7], laparoscopic gastrectomy began to be used by many surgeons around the world [5, 11]. In Japan, new laparoscopic procedures, such as laparoscopic wedge resection (LWR) and intragastric mucosal resection (IGMR), have been developed for the management of patients with early gastric cancer [14, 15]. Because of the improved outcome achieved with laparoscopic procedures for early gastric cancer, indications for laparoscopic procedures have been expanded from early to advanced gastric cancer.

Herein, we review the current indications for, techniques pertaining to, and outcomes of laparoscopic procedures for gastric cancer, including LWR, IGMR, and LADG in Japan.

I. Laparoscopic local resection of the stomach

Laparoscopic local resection of the stomach has been performed in Japan since 1994 for minimally invasive management of early gastric cancer. One technique is LWR, developed by Ohgami et al. [15], and the other is IGMR developed by Ohashi [14].

Indications

Pathologic examination of early gastric cancers reveals the presence of nodal metastasis in 2–3% of mucosal carcinomas and 15–20% of submucosal carcinomas [18, 26]. Lymphatic vessel invasion, histological tumor ulceration, and tumor diameter (> 30 mm) are independent factors predicting regional lymph node metastasis [24]. The data suggest that most early carcinomas are located only in the gastric wall and that local resection of the gastric wall is adequate for clearance. Theoretically, laparoscopic local resection can be applied to treat early gastric cancer that shows no risk factors for lymph node metastasis (Table 1). Ohgami et al. reported the following indications for LWR: (1) preoperative diagnosis of mucosal cancer, (2) diameter < 25 mm for

Table 1. Laparoscopic surgery for gastric cancer in Japan

	Laparoscopic local resection		
	IGMR	LWR	Laparosopic gastrectomy (LADG)
Number of cases in Japan[a] (1991–2001)	260	1428	2600
Indication (in our department)	Early gastric cancer without risk of LN metastasis (1) Mucosal cancer: difficult to resect by EMR elevated type (<25 mm) depressed type (<15 mm) without ulceration (2) Location posterior (IGMR), except posterior (LWR)		Early gastric cancer with risk of LN metastasis (1) Mucosal cancer: elevated type (>25 mm) depressed type (>15 mm) with ulceration (2) Submucosal cancer with slight invasion
Complication rate in Japan[a]			
Intraoperative (%)	4.2	2.1	1.4
Postoperative (%)	6.5	4.6	9.7

[a] From [8]

protruding type lesions, (3) diameter <15 mm and UL (−) for depressed type lesions [15]. The procedure can be applied to a lesion located in any part of the stomach except the posterior wall. The indications for IGMR are nearly the same as those for LWR, but IGMR can be applied to a lesion located in any part of the stomach except the anterior wall. The accepted indications for IGMR are as follows: (1) mucosal carcinoma difficult to resect completely by EMR, (2) mucosal carcinoma of the elevated type (<25 mm) or depressed type (<15 mm), and (3) mucosal carcinoma located in any part of the stomach except the anterior wall [14].

Techniques

LWR. LWR is performed by the lesion-lifting method [15]. The cancerous lesion and the gastric wall around it are exposed endoscopically and laparoscopically. The abdominal wall and gastric wall near the lesion are pierced with a 12-G sheathed needle. A small metal rod with a fine wire is inserted into the stomach through the outer sheath, and the sheath is removed. The lesion is lifted by retracting the metal rod and resected with a wedge-shaped part of the stomach with the use of an endoscopic stapler. After the resected specimen is removed, the abdomen is closed.

The lesion must be removed with an adequately clear margin. To resect the lesion successfully, Altorjay et al. developed the modified lesion-lifting method called the double-lifting method [4].

IGMR. IGMR is performed as follows. Three trocars are placed in the gastric lumen, penetrating both the abdomen and stomach walls, under gastrofiberscopic and laparoscopic observation. These trocars fix the gastric wall to the abdominal wall with a balloon. After the laparoscope and two forceps are inserted into the stomach through the trocars, dots are placed to indicate the removal margin around the lesion, and mucosal resection is performed. Hemostasis is achieved by elec-

trocautery and laser. The resected specimen is extracted by gastrofiberscope. Each balloon is then deflated, and the trocars are pulled out. Each port in the stomach is sutured laparoscopically, and the abdomen is closed.

For IGMR, it is important to access the gastric lumen easily and get an optimal operative field. There are several new devices, such as the expandable sleeve [21], which can be used instead of forceps with a balloon, to provide the necessary easy access. Yamashita et al. used a Buess-type endoscope to resect the lesion with the full-thickness wall from the gastric lumen [25].

Evaluation and current status of laparoscopic local resection in Japan

After laparoscopic local resection was made possible, its use increased in the early 1990s. A survey of the Japan Society for Endoscopic Surgery, in which 1462 out of 2706 departments of endoscopic surgery responded (the response rate: 54%), revealed 1428 LWRs and 260 IGMRs were carried out between 1992 and 2001 in Japan [8] (Table 1). These data suggest that 20–30% of patients with early gastric cancer are treated by laparoscopic local resection in these departments.

There has been no study into the clinical advantages of laparoscopic local resection versus open local resection. A survey of the Japan Society for Endoscopic Surgery showed the incidence of intraoperative and postoperative complications for the last 10 years to be 2.1% and 4.6% after LWR, and 4.2% and 6.5% after IGMR, respectively [8]. The major intraoperative complications after LWR and IGMR are bleeding and gastric emptying, respectively. These do not seem to be a higher incidence of intraoperative or postoperative complications after laparoscopic procedures compared to the incidence with open procedures. Mortality rates following LWR and IGMR were both 0%.

According to the results of the survey, patients could ingest liquid on the second day, and solid food was started on the second or third postoperative day after LWR and IGMR. In our department, the time to PO

intake was two days after LWR or IGMR, and the average period of postoperative hospital stay was ~10 days. These data suggest early recovery after laparoscopic local resection.

There are few reports of survival and cancer recurrence after LWR and IGMR. Ohgami et al. reported two recurrences out of 111 cases treated by laparoscopic local resection [15]. In both cases, recurrence was diagnosed within 2 years after initial surgery, and the lesions were successfully treated by open gastrectomy and laser irradiation. So far, all patients in Ohgami's series have survived the 4- to 65-month follow-up period. Hiki reported that all 29 patients in his series have been recurrence-free for a follow-up period of 46 months.

We believe that both LWR and IGMR are curative and minimally invasive treatments applicable to early gastric cancer without lymph node metastasis, when the indication of these procedures is limited.

II. Laparoscopy-assisted distal gastrectomy (LADG)

Laparoscopy-assisted Billroth-I gastrectomy for early gastric cancer was first performed by Kitano et al. in 1991 [7], and the first totally laparoscopic Billroth-II gastrectomy was reported by Goh and Kum in 1992 [5]. Laparoscopic gastrectomy is still in the developmental phase around the world, whereas the use of LADG for early gastric cancer has increased significantly in Japan.

Indications

LADG was developed to treat early gastric cancer in which there is some risk of lymph node metastasis at the perigastric portion (n1) (Table 1). The guidelines for gastric cancer treatment of the Japanese Gastric Cancer Association give the indications for LADG as follows: (1) mucosal cancer without preoperatively diagnosed lymph node metastasis, (2) cancer with submucosal invasion and without preoperatively diagnosed lymph node metastasis [13]. It is sometimes difficult to diagnose lymph node metastasis preoperatively, and the rate of accuracy is very low. Therefore, in our department, the indication for LADG is determined by tumor size, depth of cancer, the presence of ulceration, and histologic type [19, 26]. Our present indications for LADG are as follows: (1) mucosal cancer of the elevated (> 25 mm) or depressed type (> 15 mm), (2) mucosal cancer with peptic ulcer, (3) remnant cancer after endoscopic mucosal resection, and (4) carcinoma with minimal submucosal invasion. These criteria account for 60% of patients with early-stage gastric carcinoma in our study series.

Technique

After the Hasson type cannula is placed at the subumbilical portion, four other ports are placed in the upper abdomen under laparoscopic observation. The greater omentum and gastrocolic ligament are dissected laparoscopically outside the epigastric arcade. The right

gastroepiploic vessels are cut at the pancreatic surface to facilitate dissection of lymph nodes at the subpyloric portion. The lesser curvature is dissected, and the left gastric vessels are divided after double ligation with clips. The left cardiac and superior gastric lymph nodes are dissected down to the distal portion of the stomach. The suprapyloric lymph nodes are also dissected after ligation of the right gastric artery. After complete laparoscopic mobilization of the lower two-thirds of the stomach, a 5-cm midline skin incision is placed just below the xiphoid. After transection of the duodenum through a small laparotomy, the distal two-thirds of the stomach containing the cancer is resected with an autostapler. The regional lymph nodes are completely dissected along with the distal portion of the stomach. Gastroduodenostomy is performed in the same way it is done in open surgery, via small laparotomy.

Evaluation and current status of laparoscopic gastrectomy in Japan

The survey of the Japan Society for Endoscopic Surgery showed that 2600 LADGs were performed from 1991 to 2001 in departments of endoscopic surgery in Japan [8] (Table 1). Since 1996, the use of LADG has rapidly increased, and 959 gastric cancers were treated by LADG in 2001. Because ~20,000 patients with early gastric cancer are estimated to be performed in Japan a year, LADG may amount to only 5% in gastrectomy for early cancer. Thus, LADG is still performed in only a limited number of hospitals in Japan, but the number has increased year by year. In a few hospitals, because of the improved outcome for patients receiving LADG, indications for LADG have expanded to include lymph node dissection (D2) [23].

The survey of the Japan Society for Endoscopic Surgery showed the mortality of LADG for the past 10 years to be 0% and also showed the LADG-associated incidence of intraoperative and postoperative complications to be 1.4% and 9.7%, respectively [8]. The major intraoperative complication is bleeding, and the major postoperative complications are gastric emptying, anastomotic leakage and wound infection. Maruyama et al. reported that the mortality and morbidity of open distal gastrectomy (ODG) with D1 lymph node dissection were 0.5% and 20.6% [12]. These data suggest that LADG is as safe as conventional ODG.

There are several reports of clinical advantages of LADG compared with ODG. Goh et al. reported that 10 of 16 surgeons in responses to questionnaires in a worldwide survey recognized the superiority of laparoscopic gastrectomy to open gastrectomy because of faster recovery, less pain, and better cosmesis [6]. We showed by retrospective study that there were several advantages to LADG in comparison to ODG, including less surgical trauma assessed by acute inflammatory index, better nutrition, less pain, rapid return of gastrointestinal function, and shorter hospital stay, with no decrease in operative curability [1]. We have shown in a small randomized study that there are some advantages including less pain and less impaired pulmonary func-

tion after LADG in comparison to ODG [9]. LADG is a better option than ODG with regard to patient's quality of life (QOL) [2]. Regarding the cost, our previous study showed that LADG is less expensive than conventional open gastrectomy (total hospital charges, ¥ 1336 × 10³ vs ¥ 1411 × 10³) because both the postoperative recovery period and the hospital stay are shorter (16.1 vs 20.5 days) [3]. But Rosin et al. pointed out problems with LADG, including complexity of the procedure and long operation time [16]. A multicenter randomized controlled trial is needed to confirm the clinical advantages of LADG.

In our series, 116 LADGs with regional lymph node dissection (D1) were performed over 10 years [10]. All patients, except one who died of cerebral bleeding, were alive without recurrence or port-site metastasis at the mean follow-up period of 45 months. Although there are no other data on survival and recurrence after LADG, we believe that LADG is a curative procedure. The lower complication rate and lower recurrence rate of LADG might be caused by not only the strict indications for LADG but also the improvement in technique on the instruments, such as laparoscope and laparoscopic coagulation shears, or surgical skill. Now, a few institutes in Japan have tried to treat advanced gastric cancer laparoscopically.

Conclusions

Laparoscopic gastrectomy for gastric cancer is still in the developmental phase in Japan. Since 1991, three laparoscopic procedures, LWR, IGMR, and LADG, have been used in Japan, and they have been widely accepted for the past 10 years. The indication for LWR and IGMR is mucosal cancer without risk of lymph node metastasis, and that for LADG is early gastric cancer with a risk of perigastric lymph node metastasis (n1). We believe that laparoscopic procedures are useful for the treatment of patients with early gastric cancer because of the minimal invasiveness, decrease in pain, and early recovery. If the advantages can be confirmed in one or more multicenter randomized control studies of the long-term outcome of patients undergoing laparoscopic gastrectomy for gastric cancer, the procedure will come into wide acceptance and use.

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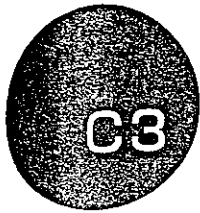
腹腔鏡下手術

これは困ったぞ,どうしよう！
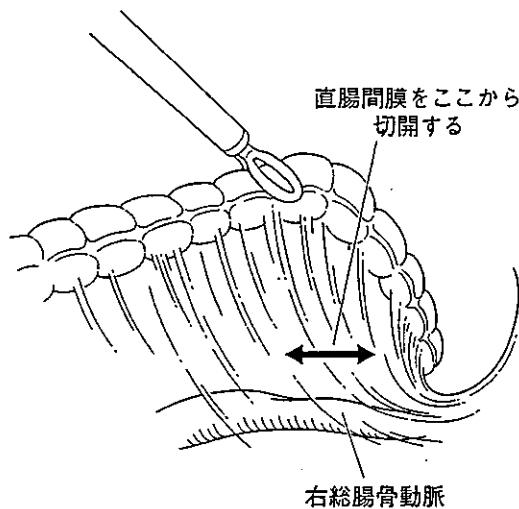
亀田総合病院特命院長補佐・主任外科部長・
内視鏡下手術センター長　加納宣康　編著

中外医学社

3．直腸切除術……………………………………………………………〔宗像康博〕　59

4．経肛門的内視鏡下手術（TEM/TES）…………………………………〔金平永二〕　62

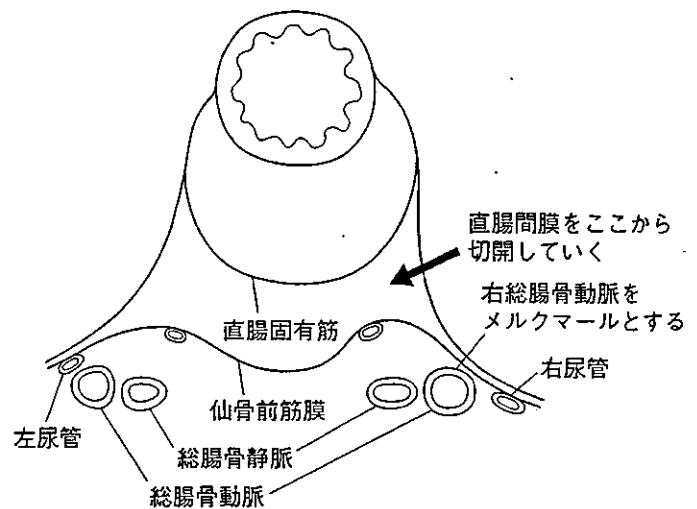## 5．虫垂切除術……………………………………………………〔吉川征一郎・福永正氣〕　66

C3 直腸切除術

Q1 剥離層がうまく同定できない．何を目安にしたらいいのだ？

A S状結腸を充分に挙上して，直腸間膜右側を緊張させる．右総腸骨動脈を確認し，その腹側の直腸間膜を切開し，鈍的に剥離すると，そこは直腸固有筋膜と骨盤筋膜の間の粗な部分であり，その層を頭側尾側に広げると剥離すべき層になる（図1, 2）．腸間膜を充分に牽引することがコツである．

直腸間膜をここから
切開する

右総腸骨動脈

図1 正しい剥離層の見つけ方
（内側アプローチ）

直腸間膜をここから
切開していく

右総腸骨動脈を
メルクマールとする

右尿管

直腸固有筋

仙骨前筋膜

左尿管

総腸骨静脈

総腸骨動脈

図2 正しい剥離層の見つけ方（断面図）

Q2 尿管が同定できない．どうしよう！

A 内側アプローチでは上記の剥離層を腹部大動脈前面から左側の方へ広げていくと，左総腸骨動脈と交叉する左尿管を容易に確認できる（図3）．外側よりのアプローチではToldtのfusion fasciaに沿って内側に剥離を進めると後腹膜下筋膜の背側に尿管を透見できる（図4）．

Q3 尿管に熱が伝わって一部白くなっている．どうしよう！

A 尿管の一部が白くなっている程度では問題はないと思われるが，尿管表面の血管が障害され，循環障害がある場合や尿管が全周にわたり変性している場合は狭窄や穿孔の危険があるので，要注意である．泌尿器科に依頼して，膀胱鏡下に尿管スプリントを留置する．

Q4 尿管が一部切れてしまった．どうしよう！

A 泌尿器科に依頼して吻合し，尿管スプリントを留置する．尿管の挫滅が強かったり，尿管の循環障害が合併していると，障害された尿管の切除を要することがあるので，経験豊かな泌尿器科医のアドバイスが必要である．
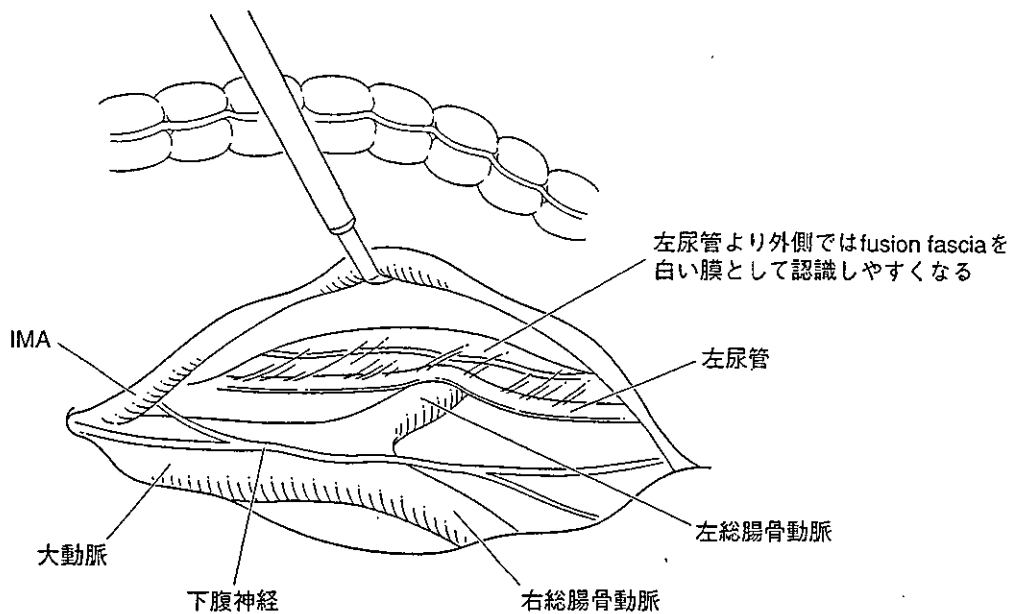
左尿管より外側ではfusion fasciaを
白い膜として認識しやすくなる

左尿管

IMA

左総腸骨動脈

大動脈

下腹神経　　　右総腸骨動脈

〔図3〕　内側アプローチでの尿管の見つけ方

fusion fascia
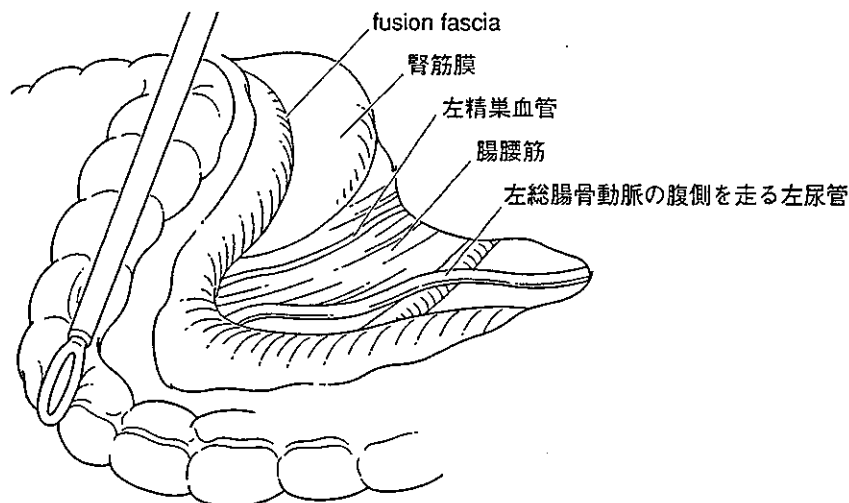
腎筋膜

左精巣血管

腸腰筋

左総腸骨動脈の腹側を走る左尿管

〔図4〕　外側アプローチでの尿管の見つけ方

Q5　脂肪が多くて閉口する．経験豊富な人たちはどうやっているのだろう？

　　A　肥満のために開腹移行することはほとんどないが，肥満者でいちばん困難なことは，腹壁が厚いためにトロカーを刺入したあとのトロカーの角度の自由度（可動範囲）が制限されることである．腹腔内での操作は正しい剥離層で手術を進める限り，時間はかかっても不可能なことはない．良好な視野を得るためには，トロカーを追加する．ハンドアシストを考慮する．

Q6　重力を使って腸管を移動させて術野を作れというが，いったいどこまで傾けてもいいものだろう？　安全な固定方法は何か？

　　A　鏡視下専用の手術台ではなくてもかなりのティルトは可能である．われわれは下肢をレビテータで固定し，特注の（現在は製品化されている）側板を使用している（図5）．手術台のティルトだけに頼らず，トロカーの追加やハンドアシストも考慮する．
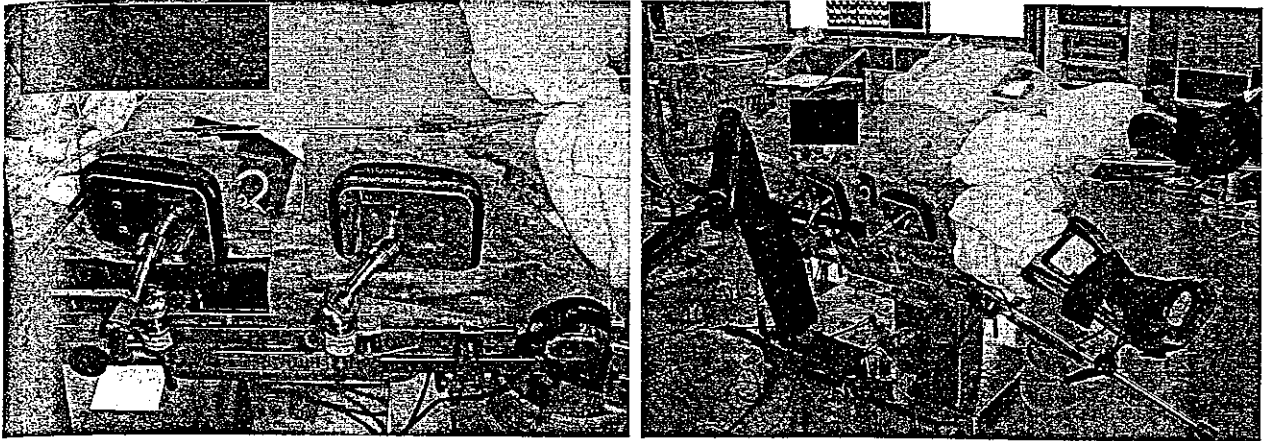
〔図5〕特注の側板による患者の保持

Q7　直腸を endostapler で切ったが，緊張がかかった状態で切ったので，一部が開いていないか心配だ．どうしよう！

　　　A　リークテストを行う．口側を腸鉗子や綿テープでクランプし，肛門より空気を注入する．もし，リークが認められたら，さらに肛門側を再切除できる場合はステープラで再度縫合切離する．下部直腸で再度の切除が困難な場合は，経肛門的手縫い吻合に変更する．

Q8　直腸を引っ張って剥離しているうちに一部穴があいた．どうしよう！

　　　A　さらに肛門側を剥離して穿孔部の肛門側でステープラを使って直腸を切離する．下部直腸で穿孔してしまい，上記の対応ができない場合は，直腸を切離してしまい，経肛門的に手縫い吻合する（超低位前方切除とする）．

Q9　直腸後面の血管処理を超音波凝固切開装置でやっていたら直腸が焼けて一部白くなっている．ここで切離して大丈夫だろうか？　また，超音波凝固切開装置だけで切ると不安だが，どうしよう！クリップを使うと吻合の時じゃまになるかもしれない．

　　　A　下部直腸で切離する場合は，直腸の剥離には超音波凝固切開装置だけで充分である．クリップはステープラの誤動作の原因となるので，切離線近くで使用してはならない．

Q10　DST で吻合したら，吻合後に抜けなくなった．どうしよう！

　　　A　リニアステープラをサーキュラーステープラで打ち抜けないときに起こり得る．アンビルヘッドをリリースし，ステープラ本体を抜去した後，経肛門的にステープルラインを切離して，アンビルヘッドを除去する．強引に引き抜くと吻合線を損傷する．

Q11　DST で吻合したら，帰室してから大量に下血した．どうしよう！

　　　A　吻合線からの出血と考える．まず，止血薬の投与，冷生食での洗浄，トロンビン末の直腸内散布を行う．それでも出血が止まらない時は，内視鏡的にクリップで止血する．

〔宗像康博〕

Laparoscopic Surgery:
Beyond Mere Feasibility

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Increased peritoneal dissemination after laparotomy vs pneumoperitoneum in a mouse cecal cancer model

H. Takeuchi, M. Inomata, K. Fujii, S. Ishibashi, N. Shiraishi, S. Kitano

Department of Surgery I, Faculty of Medicine, Oita University, 1-1 Idaigaoka, Hasama-machi, Oita 879-5593, Japan

Abstract

Background: The effect of carbon dioxide (CO_2) pneumoperitoneum on the liberation of cancer cells from the primary tumor is not clear. This study investigated the influence of laparotomy versus CO_2 pneumoperitoneum on the progression of colon cancer with serosal invasion in a mouse model.

Methods: Pieces of human colon adenocarcinoma (HT29) tumor were implanted in the cecal wall of 45 BALB/c nude mice. Each mouse underwent one of three procedures: laparotomy, CO_2 pneumoperitoneum, or anesthesia (control). Three weeks later, the size and weight of cecal tumors, the number of nodules, and the tumor volume score of peritoneal dissemination were examined. Another 45 mice were treated in the same way. The cecal tumor was resected on days 1, 3, or 5 after treatment. Total RNA was isolated from the resected tumors. The expression of E-cadherin and beta-1 integrin messenger RNA (mRNA) was examined by semiquantitative real-time reverse transcriptase–polymerase chain reaction assay.

Results: Significantly more nodules of peritoneal dissemination were found in the laparotomy group than in the control group ($p < 0.05$). The tumor volume score of peritoneal dissemination in the laparotomy group was significantly higher than in the other two groups ($p < 0.05$). The expression of E-cadherin mRNA at day 5 in the laparotomy group was significantly less than in the other two groups ($p < 0.05$). There were no differences in beta-1 integrin among three groups.

Conclusions: Peritoneal dissemination was more extensive after laparotomy than after CO_2 pneumoperitoneum in a mouse model of cecal cancer with serosal invasion. Decreased expression of E-cadherin mRNA in tumors after laparotomy, but not after CO_2 pneumoperitoneum, may be associated with the increase in peritoneal dissemination.

Laparoscopic surgery has been applied to many patients with colorectal cancer [1, 12, 14, 22]. It is considered less invasive and less immunosuppressive than conventional open surgery [12, 14]. Recently, the indications for laparoscopic resection have been expanded to include not only the early stage, but also the advanced stage of malignancy. However, the influence of the laparoscopic procedure on the prognosis of patients with malignancy is unclear.

Peritoneal dissemination is an important prognostic factor in colorectal cancer. Surgery is indicated for advanced colorectal cancer with serosal invasion before peritoneal dissemination occurs. Therefore, several animal studies have investigated the effects of carbon dioxide (CO_2) pneumoperitoneum induced for laparoscopic surgery on port-site seeding and peritoneal dissemination [3, 9, 16]. Instrument manipulation and mechanical tumor spillage seem to play the major role in cancer seeding and dissemination in laparoscopic surgery [3, 17]. On the other hand, morphologic study using electron microscopy showed the typical changes of mesothelial cells after CO_2 pneumoperitoneum and laparotomy [18, 21], suggesting the direct influence of mesothelial cells on the adhesion molecules by these surgical procedures. It therefore is also critical to clarify the effect of CO_2 pneumoperitoneum and laparotomy on the liberation of cancer cells from primary tumor with serosal invasion but without peritoneal dissemination.

In the current study, we investigated and compared the influence of CO_2 pneumoperitoneum and that of laparotomy on the progression of colorectal cancer with serosal invasion in a nude mouse model from the viewpoint of adhesion molecules expression.

Correspondence to: H. Takeuchi

Table 1. Tumor volume score

Points	Nodule diameter
0	< 1 mm
1	≥1 to < 2 mm
2	≥2 to < 3 mm
3	≥3 to < 4 mm

Table 2. Primer sequences for the reverse transcriptase–polymerase chain reaction

Molecule	Sequence (5′–3′)
E-cadherin	Sense	TCC CAT CAG CTG CCC AGA AA
	Antisense TGA CTC CTG TGT TCC TGT TA
Beta-1	Sense	GTT ACA CGG CTG CTG GTG TT
integrin	Antisense CTA CTG CTG ACT TAG GGA TC
GAPDH	Sense	GGC AGA GAT GAT GAC CCT TTT GGC
	Antisense AAG GTG AAG GTC GGA GTC AAC G

GAPDH, glyceraldehyde phosphate dehydrogenase

Materials and methods

Male 7-week-old BALB/c nude mice were kept under standard laboratory conditions with free access to food and water before and after surgery. All procedures were performed according to the Guidelines for Animal Experimentation of Oita University. An HT29 human colon adenocarcinoma cell line was grown in RPMI 1640 medium (Gibco BRL; Life Technologies, Rockville, MD, USA) supplemented with 10% fetal bovine serum (Gibco BRL) and an antibiotic–antimycotic agent containing 100 IU/ml penicillin, 0.1 mg/ml streptomycin, and 2.5×10^4 mg amphotericin B (Gibco BRL). The cells were cultured in dishes in a 5% CO_2 atmosphere at 37°C.

Cecal cancer model

This study was performed with a modified cecal cancer model [6]. The mice were anesthetized with diethyl ether and inoculated with 0.1 ml of the tumor suspension (1×10^6 cells). Three weeks later, a subcutaneous tumor was resected aseptically from each mouse. Necrotic tissue in the resected tumor was cut away, and the remaining healthy tumor tissue was scissor-minced into 50-mg pieces in Hank's balanced salt solution. A second group of mice was anesthetized the same way, and tumor pieces were fixed on the serosal surface of the murine cecal wall.

Experiment 1

Tumor pieces were implanted in the cecal wall of 45 mice. Three weeks later, the mice were randomly divided into a laparotomy group ($n = 15$), a CO_2 pneumoperitoneum group ($n = 15$), and an anesthesia (control) group ($n = 15$). For the CO_2 pneumoperitoneum group, we used a convenient murine pneumoperitoneum model that we have described previously [19]. With the mice under anesthesia with diethyl ether, CO_2 pneumoperitoneum was created and maintained for 30 min with CO_2 insufflations at 5 mmHg.

Three weeks later, all the mice were killed using anesthesia overload. Cecal tumors were resected, and tumor size and weight were measured. Peritoneal dissemination was assessed by the number of nodules larger than 1 mm in diameter and by the tumor volume score (Table 1).

Experiment 2

Tumor pieces were implanted in the cecal wall of another 45 mice. Three weeks later, the mice were randomly divided into three groups the same as in the first experiment. The mice were treated as previously described and killed per each three groups on days 1 ($n = 5$), 3 ($n = 5$), or 5 ($n = 5$) after surgery. A tissue sample from the cecal tumor of each mouse was frozen immediately in liquid nitrogen and stored at −80°C until extraction of total RNA. Total RNA was isolated from the cecal tumors by the acid guanidinium thiocyanate–phenol–chloroform extraction procedure [4], complementary DNA (cDNA) was synthesized by reverse transcription from 2.5 μg of total RNA. A real-time polymerase chain reaction (PCR) assay was performed with a LightCycler (Roche Diagnostics, Mannheim, Germany) in a total volume of 20 μl, to which was added 2 μl of 10X reaction buffer (Taq polymerase, diethylnitrophenyl thiophosphates, magne-
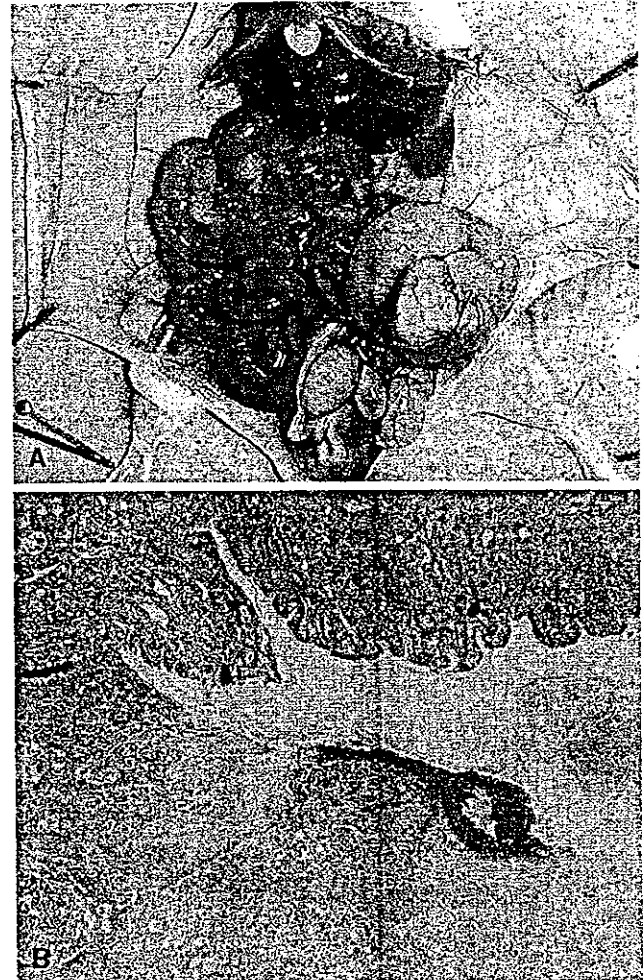

Fig. 1. A Photograph of an implanted cecal tumor. B Hematoxylin and eosin staining of an implanted cecal tumor. The implanted cecal tumor invaded to the mucosa from the serosa in 3 weeks.

sium chloride, SYBR Green; Roche Diagnostics), and 2 μl of cDNA. Magnesium chloride and each oligonucleotide primer (Table 2) were added to a final concentration of 4 mmol/l and 0.5 μmol/l, respectively. Real-time PCR was performed with an initial denaturation step of 10 min at 95°C, followed by 40 cycles of 15 s at 95°C, 10 s at annealing temperature (glyceraldehyde phosphate dehydrogenase 58°C; E-cadherin, 60°C; beta-1 integrin, 60°C), and product length (bp)/25 s at 72°C. At the end of each cycle, the fluorescence emitted by the SYBR Green was measured. The relative fluorescence of each messenger RNA (mRNA) was normalized to the fluorescence of GAPDH for semiquantification.
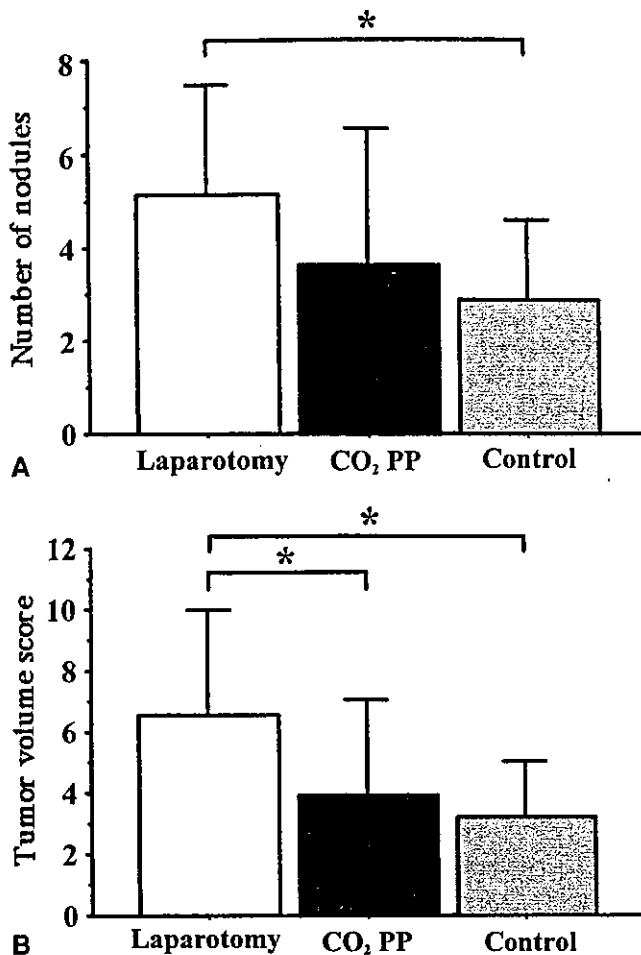
Fig. 2. a The number of nodules of peritoneal dissemination. b Tumor volume score of peritoneal dissemination. PP, pneumoperitoneum ($*p < 0.05$).

Table 3. Volume and weight of the cecal tumor

	Laparotomy	CO_2 PP	Control	p value
Volume (mm^3)	890 ± 416	744 ± 341	752 ± 265	NS
Weight (mg)	985 ± 435	923 ± 435	903 ± 229	NS

CO_2 PP, carbon dioxide pneumoperitoneum; NS, not significant

Statistical analysis

All data are expressed as the mean ± standard deviation. Statistical analysis was performed using the Mann–Whitney U test, and a p value less than 0.05 was considered statistically significant.

Results

We confirmed by histologic study that an implanted cecal tumor in this model invaded from the serosal layer to the mucosal layer in 3 weeks (Fig. 1a and b). After 3 weeks, peritoneal dissemination was identified macroscopically as a small nodule at the surface of the small intestine.

A significantly larger number of peritoneal dissemination nodules was observed in the laparotomy group
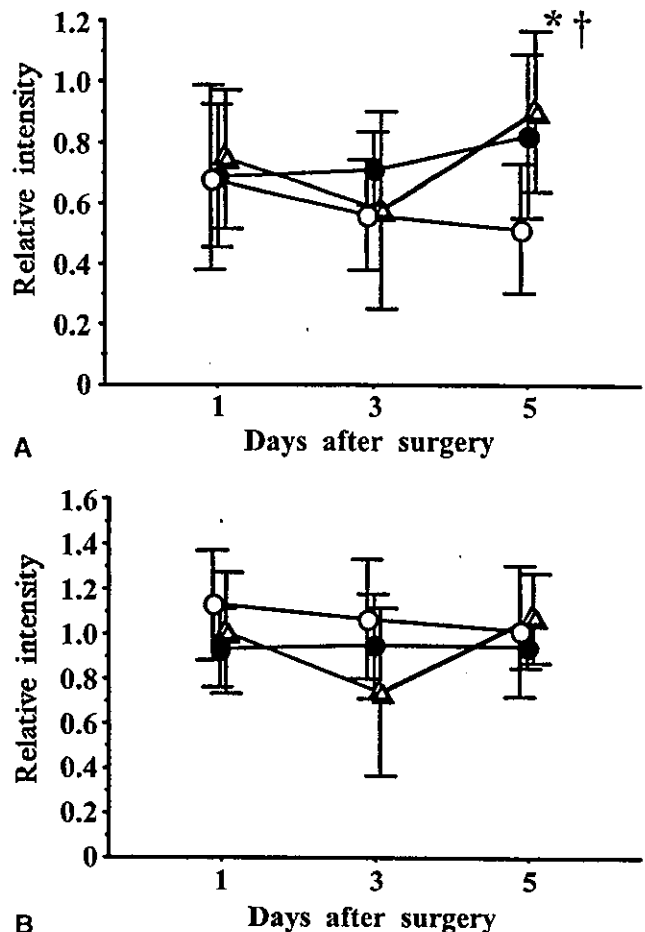

Fig. 3. Expression of E-cadherin (a) and beta-1 integrin (b) messenger RNA (mRNA) in mouse tumor in the three groups, as measured by real-time reverse transcriptase–polymerase chain reaction. The relative expression of each mRNA is normalized to the expression of glyceraldehyde phosphate dehydrogenase for semiquantification. O laparotomy, ●, CO_2 pneumoperitoneum, Δ control. ($*p < 0.05$ laparotomy vs CO_2 pneumoperitoneum, $†p < 0.05$ laparotomy vs control).

(5.13 ± 12.33) than in the control group (2.87 ± 2.90) ($p < 0.05$) (Fig. 2a). The mean tumor volume score of peritoneal dissemination was significantly higher in the laparotomy group (6.53 ± 3.42) than in either the CO_2 pneumoperitoneum group (3.93 ± 13.04) or the control group (3.20 ± 1.82) ($p < 0.05$) (Fig. 2b). The volume and weight of the cecal tumor did not differ significantly among the three groups (Table 3).

The expressions of E-cadherin and beta-1 integrin mRNA on days 1, 3, and 5 after surgery are shown in Fig. 3. The expression of E-cadherin mRNA on day 5 in the laparotomy group was significantly depressed as compared with that in the CO_2 pneumoperitoneum and control groups (Fig. 3a). The expression of beta-1 integrin mRNA on each day did not differ significantly among the three groups (Fig. 3b).

Discussion

In this study, we found that peritoneal dissemination was more frequent after laparotomy than after CO_2

pneumoperitoneum in a nude mouse cecal implantation model. Our findings suggest that the increased peritoneal dissemination could result from the liberation of cells from the primary tumor. Several studies have demonstrated less impaired immunity after CO_2 pneumoperitoneum than after laparotomy [7]. Using nude mice, Volz et al. [21] showed the morphologic changes of mesothelial cells after surgical procedures, suggesting the possibility that these morphologic effects did not result from changed immunity by CO_2 pneumoperitoneum. Therefore, a nude mouse model was used in our study to clarify the direct effects of surgical procedures on the adhesion molecules of cancer cells.

There are three steps in the formation of peritoneal dissemination: liberation of cancer cells from the primary tumor, implantation to the peritoneum, and proliferation in the implanted area. Although we found several animal studies on the effect of CO_2 pneumoperitoneum on peritoneal implantation and proliferation [9, 16], no study was found that compared the liberation of cancer cells from the primary tumor after CO_2 pneumoperitoneum and after laparotomy. To examine the peritoneal implantation and proliferation after CO_2 pneumoperitoneum, an animal model with injection of cancer cells into the peritoneal cavity often is used [9, 16]. To study the liberation of cancer cells from the primary tumor after CO_2 pneumoperitoneum, we used the animal model with cecal cancer established previously by Furukawa et al. [6]. Using this animal model, cecal cancer with serosal invasion was identified in all mice 3 weeks after implantation of a tumor piece, and peritoneal dissemination also occurred in 42 of 45 mice 6 weeks after implantation.

The effect of CO_2 pneumoperitoneum on tumor growth and peritoneal dissemination still is controversial. Using a mouse model, Da Costa et al. [5] and Gitzelmann et al. [7] showed that subcutaneous tumor growth was greater after laparotomy than after CO_2 pneumoperitoneum. Bouvy et al. [2] used a rat model to show that tumor growth in the abdominal wall was greater after laparotomy than after CO_2 pneumoperitoneum. Using a rat model, Gutt et al. [8] showed that peritoneal tumor growth was greater after laparotomy than after CO_2 pneumoperitoneum. However, using a WAG rat model, Hubens et al. [10] found no significant difference between peritoneal tumor growth after CO_2 pneumoperitoneum and after laparotomy. In our study using nude mice, the size and weight of the cecal tumor in the CO_2 pneumoperitoneum group did not differ from that in the laparotomy group. Further study is necessary to clarify the factors influencing tumor growth after laparotomy, such as growth factors and immunity.

Several studies have investigated the effects of CO_2 pneumoperitoneum on port-site seeding and peritoneal dissemination. Le Moine et al. [15] reported that laparoscopic cecal resection significantly increased the incidence of a diffuse carcinomatosis, even when performed for locally noninvasive tumors, and emphasized the risk of increased peritoneal dissemination after laparoscopic surgery from manipulation of cancer cells in surgical procedures. Brundell et al. [3] and Texler et al. [20] also demonstrated by in vitro and in vivo experiments that

instrumental manipulation, mechanical tumor cell spillage, and local metabolism played the important role in port-site seeding of cancer cells after CO_2 pneumoperitoneum. On the other hand, morphologic studies with electron microscopy by Suematsu et al. [18] and Volz et al. [21] showed that peritoneal mesothelial cells were exfoliated and the basal membrane was exposed soon after surgical procedures. These changes were more intensive after laparotomy than after CO_2 pneumoperitoneum, suggesting that surgical procedures damage adhesion molecules of mesothelial cells. It is possible that adhesion molecules of cancer cells on the surface of the tumor also may be affected by surgical procedures. We showed in the current study that the tumor volume score of peritoneal dissemination in the laparotomy group was significantly higher than in either the CO_2 pneumoperitoneum group or the control group, possibly because of a decrease in E-cadherin cellular adhesion molecules.

E-cadherin is known as a main adhesion molecule for epithelial cell–cell interaction. Recent studies have shown that deletion of E-cadherin contributes to hematogenous metastasis and peritoneal dissemination of a tumor [11, 13, 23]. In the current study, the expression of E-cadherin mRNA was depressed on day 5 after laparotomy, as compared with the expression on day 5 after CO_2 pneumoperitoneum. Although the quantity and function of E-cadherin protein in the tumor were not measured in this study, the expression of E-cadherin mRNA was shown to be decreased on day 5 after laparotomy, as compared with expression on day 5 after CO_2 pneumoperitoneum. These data suppose the possibility that decreased E-cadherin in a tumor after laparotomy enables cancer cells to detach easily from the primary tumor and implant into the peritoneum.

In conclusion, we observed more extensive peritoneal dissemination after laparotomy than after CO_2 pneumoperitoneum in a mouse model of cecal cancer with serosal invasion. The decreased expression of E-cadherin mRNA in tumors after laparotomy but not after CO_2 pneumoperitoneum may be associated with the increase in peritoneal dissemination. Clinically, the long-term survival of patients who have undergone laparoscopic surgery for colon cancer is not clear, but our animal study suggests that laparoscopic surgery for colon cancer with serosal invasion is acceptable in terms of peritoneal dissemination.

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臨床応用レベルでの話題
悪性腫瘍への腹腔鏡下手術の現況

猪 股　雅 史　　北 野　正 剛　　白 石　憲 男

臨床応用レベルでの話題
悪性腫瘍への腹腔鏡下手術の現況
The current status of laparoscopic surgery for malignant diseases

猪 股 雅 史　　北 野 正 剛**　白 石 憲 男*
INOMATA Masafumi　　KITANO Seigo　　SHIRAISHI Norio

1987年に胆嚢摘出術に導入されて以来，腹腔鏡下手術は，胃癌・大腸癌・肝臓癌などの悪性疾患においても，低侵襲手術(Minimally invasive surgery)というカテゴリーを確立し，患者のQOLを重視する社会のニーズと相まって，この10数年で急速な普及をとげた．しかしながら各術式とも短期成績の評価から，その低侵襲性と安全性が明らかになったものの，進行癌に対する根治性や患者QOLなど長期成績については未だ明確でなく，EBMに基づいて適応が決定されているとは言い難い．

新たな機器の開発とともに手技の標準化あるいは安定化が図られた現在，全国レベルでの質の高い臨床研究の遂行によって長期成績を明らかにすることが求められている．

はじめに

腹腔鏡下手術は1987年胆嚢摘出術に導入されて以来，「key hole surgery」や「Nintendo operation」などと呼ばれ，「痛まず・傷が小さく・早く家に帰れる」手術として注目を集めた．これは，400年前にAmbrois Pareによって始められた近代外科学の歴史のなかで革命的な出来事といっても過言ではない．この腹腔鏡下手術は，患者のQOLを重視する近年の医療，社会のニーズに合致し，「低侵襲手術(Minimally invasive surgery)」というカテゴリーを確立して，この10数年で驚くばかりの急速な発展をとげた．その適応も，当初は胆石症や自然気胸，逆流性食道炎，鼠径ヘルニアなど良性疾患が主体であったが，

1990年代前半より胃癌・大腸癌をはじめとし，肺癌，食道癌，肝癌などの悪性疾患にも拡大されてきた．

本稿では，急速に普及してきた内視鏡外科手術のなかで，悪性疾患に対する腹腔鏡下手術の現況と問題点，さらに将来展望について述べたい．

I. 腹腔鏡下手術の動向

腹腔鏡下手術の動向については，日本内視鏡外科学会の第6回全国アンケート調査結果(2002年実施)から，その適応疾患，術式の種類および実施症例数のいずれもこの10年間に急速に増加していることが分かる(図1)[1]．最も症例数の多い胆
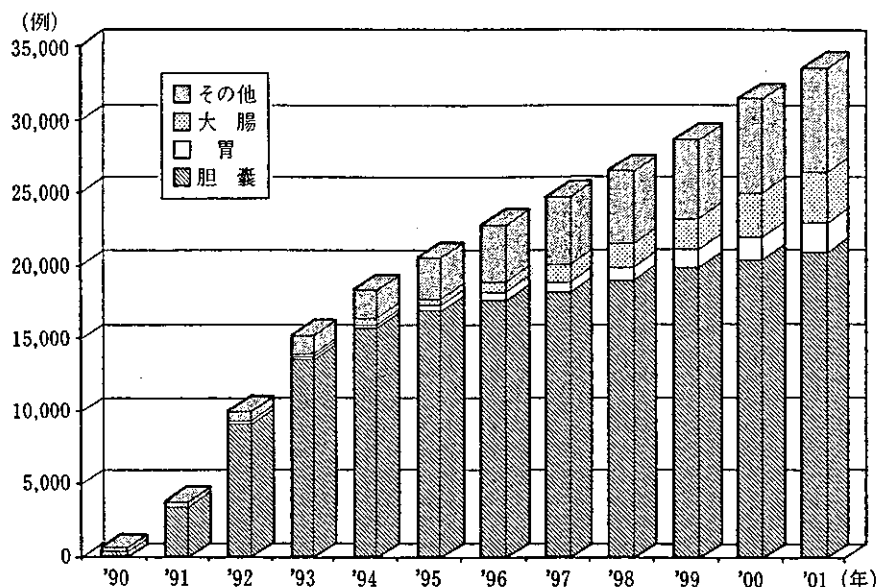
図1 わが国における腹腔鏡下手術の動向
(日本内視鏡外科学会第6回アンケート調査報告)

石症や自然気胸などの良性疾患は，開腹開胸手術に取ってかわり第一選択の術式としてすでに確立されたといえる．胃癌・大腸癌・肺癌などの悪性疾患については，これまで早期癌が対象とされていたが，最近ではその適応が進行癌へと広がっている．肝癌では，凝固壊死療法（RFA や MCT）の普及と相まって肝切除術も次第に普及しつつある．また腹腔鏡下手術は，根治手術はもとより，癌の腹膜播種などの進行度診断や緩和手術においてもその利点が生かされ多くの癌患者に用いられている．

以下，各疾患における腹腔鏡下手術の現況について述べたい．

II. 胃癌に対する腹腔鏡下手術

1. 術式の開発と現況

本邦で発生頻度の高い胃癌に対して，わが国に腹腔鏡手術が導入された翌年の1991年より日本独自の新しい術式が開発されてきた[2]-[4]．大上らの開発した腹腔鏡下胃局所切除術（LWR）は，腹壁と胃壁を貫く T 型ファスナーを用いて病変を吊り上げ，自動縫合器を用いて腹腔内にて胃壁を楔状切除するものである[3]．術後の軽微な疼痛，早期社会復帰，十分な残胃容量など患者にとって有用な術式である．腹腔鏡下胃内粘膜切除術（IGMR）は，腹腔鏡と鉗子を胃内に進め，病変部の粘膜切除を行う方法である[4]．胃の後壁病変に対して有用な術式であると報告されているが，手技的困難さから症例は限られている．今後，IT（insulation-tipped diathermic）ナイフなどを用いた一括切除可能な内視鏡的粘膜切除（EMR）法の改良と普及によって，リンパ節郭清を伴わないこれら術式の適応症例は次第に減少してゆくものと思われる．一方，D1+α の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年にわれわれが開発した術式である[2]．まず，腹腔鏡下操作にて胃周囲のリンパ節郭清と胃の授動を十分に行った後，上腹部に約5 cm の小開腹創をおき胃を体外に取り出す．通常の開腹手術同様，直視下に幽門側胃切除術，Billroth I 法による再建を行い，吻合部を腹腔内へもどし，手術を終了するものである．D1+α リンパ節郭清を伴う LADG の現時点での適応は，EMR 困難な M 癌および高度浸潤例を除いた4 cm 以下の SM 癌としており，その施行症例は年々倍加している状況
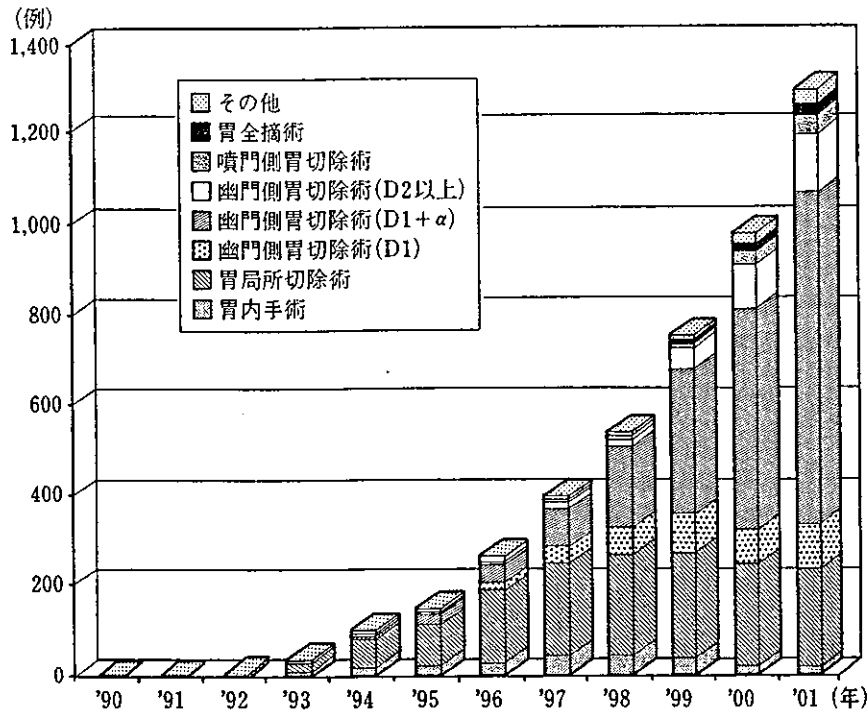
図2　胃癌に対する腹腔鏡下手術
(日本内視鏡外科学会第6回アンケート調査報告)

・である(図2).

2．LADG の有用性の評価

この術式の有用性に関しては，従来の開腹手術との症例対照研究やランダム化比較試験の結果が報告されている．表1にLADGの有用性をまとめた[5]-[8]．これらの評価から，LADGは根治性と低侵襲性を兼ね備え，術後QOLの向上や医療経済に貢献する有用な術式といえよう．

III．大腸癌に対する腹腔鏡下手術

1．術式の開発と現況

1991年Jacobsらが世界ではじめて腹腔鏡下大腸切除術を報告し，本邦では，その2年後に初めての施行例が報告された．当初は内視鏡的ポリープ適除の適応外となった大きなポリープや一部の早期癌に対して施行されていたが，手術手技と器具の改良によってリンパ節郭清手技が飛躍的に進歩し，その適応は早期癌から進行癌へと拡がり，

表1　LADG の有用性(開腹手術との比較)

1. ランダム化比較試験(文献8を改変)	
(1)手　　術	出血量が少ない
(2)術後経過	歩行開始が早い
	排ガスまでの期間が短い
	VASスコア(3POD)が良好
	努力肺活量(3POD)が高い
2. 症例対照研究(文献5-7を改変)	
(1)手　　術	出血量が少ない
(2)術後経過	鎮痛薬の使用量が少ない
	排ガスまでの期間が短い
	飲水開始日が早い
	発熱期間が短い
	体重減少が軽度
	術後在院日数が短い
(3)血液検査	WBCの上昇が軽度
	顆粒球数の上昇が軽度
	CRPの上昇が軽度
	IL-6の上昇が軽度
	Albの低下が軽度
(4) QOL	体重減少の程度が軽い
	嚥下困難感が軽い
	胸焼けが少ない
	他の人に勧められる手術
(5)医療費	看護と病棟・食事に関する費用が少ない