Retrospective examination of the incidence of surgical site infection of laparoscopic versus open surgery for colon cancer

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<Purpose> We reviewed the incidence of SSI of laparoscopic versus open surgery for colon cancer. **<Methods>** We classified 511 examples who have colon cancer in laparoscopic-surgery group (Lap group, 253 cases) and open-surgery group (Open group, 258 cases) and reviewed an incidence of wound infection and an intra-peritoneal abscess. In addition, we reviewed an incidence of wound infection in a border in 180 minutes in operation time. **<Results>** We recognized a significant difference for an incidence of wound infection, but that of intra-peritoneal abscess did not have the difference. In the case of less than 180 minutes operation time, an incidence of wound infection did not have a significant difference between both groups. But it was significantly low incidence in Lap group from Open group when over 180 minutes. Even examination limited for Dukes classification B period and C period was similar results. **<Conclusion>** Laparoscopic surgery was lower in an SSI incidence than open surgery and there was little influence of operation time.

Laparoscopic Colectomy for Colorectal Cancer Patients with Previous Abdominal Surgery

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ABSTRACT

Background/Aims: Laparoscopic colectomy has been widely accepted as a standard operation for colorectal cancer. The use of this procedure for patients with previous abdominal surgery is now well established. The aim of this study was to evaluate the peri-operative and long-term outcomes of such patients, and to compare them to patients without previous surgery.

Methodology: Data on a consecutive 121 cases of laparoscopic colectomy performed for colorectal cancer from 1995-1999 in Shikoku Cancer Center were analyzed retrospectively for peri-operative and long-term outcomes.

Results: Twenty one cases (17%) of laparoscopic colectomy were performed for colorectal cancer patients with previous surgery. Although the operation time for the previous surgery group was significantly longer than that of the control group, there was no significant difference in the peri-operative complications and the overall survival between the 2 groups.

Conclusions: Although the previous abdominal surgery increases the time it takes to perform the laparoscopic colectomy, the peri-operative and long-term outcomes were comparable to those from patients without previous surgery.

KEY WORDS:
Laparoscopic colectomy; Previous abdominal surgery; Colorectal cancer

INTRODUCTION

Laparoscopic colectomy has been widely accepted as a standard operation for colorectal cancer. This is due to both improvements in the method and to the progressive reduction in contra-indications. Previous abdominal surgery, which was once reported as a contraindication, is now becoming an indication for laparoscopic surgery if surgeons use good judgment in patient selection and meticulous surgical techniques (1-5). Although it has been reported that peri-operative outcomes are acceptable in laparoscopic colorectal cancer surgery for such patients, none of the previous studies showed a long-term outcome after the surgery for such patients (2). Laparoscopic colectomy has been performed on colorectal cancer patients with previous surgery since 1995. In this study, the peri-operative and long-term outcomes of laparoscopic colectomy were evaluated for these patients, and compared them with colorectal cancer patients without previous surgery during the same period.

METHODOLOGY

From 1995-1999, 121 cases of laparoscopic colectomy for colorectal cancer patients were performed in Shikoku Cancer Center. The patients' demographics, the nature of their disease, the operative details including the operating time, blood loss, and conversion, and the post-operative complications and the long-term outcomes were prospectively collected. Previous abdominal surgery was defined as any type of open abdominal procedures that could potentially lead to peritoneal adhesions. Laparoscopic colectomy

TABLE 1 Patient Demographics

	Previous surgery (n=21)	Control (n=100)	Total (n=121)	*p*-value
Sex				
Male	9 (43%)	51 (51%)	60	0.498
Female	12 (57%)	49 (49%)	61	
Age (year) Median (range)	68 (46-89)	65 (37-93)	66 (37-93)	0.572
BMI Median (range)	23 (18-29)	23 (14-30)	24 (14-30)	0.859
Location				
Cecum	2 (10%)	9 (9%)	11	0.741
Ascending colon	7 (33%)	21 (21%)	28	
Transverse colon	1 (5%)	9 (9%)	10	
Descending colon	1 (5%)	8 (8%)	9	
Sigmoid colon	5 (24%)	35 (35%)	40	
Rectum	5 (24%)	18 (18%)	23	
Duke's stage				
A	13 (62%)	53 (53%)	66	0.678
(Pathological)				
B	5 (24%)	21 (21%)	26	
C	2 (10%)	21 (21%)	23	
D	1 (5%)	5 (5%)	6	
Operation method				
Ileocecal resection	5 (24%)	15 (15%)	20	0.185
Right (hemi)colectomy	1 (5%)	16 (16%)	17	
Left (hemi)colectomy	0	5 (5%)	5	
Sigmoidectomy	4 (19%)	33 (33%)	37	
Anterior resection	5 (24%)	18 (18%)	23	
Local resection	6 (29%)	13 (13%)	19	

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TABLE 2 Nature of Previous Surgery

Types of previous operation	No. of patients*
Colorectal surgery	6
Gynecologic surgery	5
Appendectomy	5
Small bowel surgery (Lysis of adhesion)	5
Cholecystectomy	3
Gastroduodenal surgery	3
Esophagectomy (reconstructed by gastric tube)	1

*Five patients had multiple previous surgeries.
All previous surgeries were open surgery.

TABLE 3 Peri-operative Outcomes

	Previous surgery (n=21)	Control (n=100)	*p*-value
Operation time (min)	175 (75-330)	155 (80-337)	0.029
Blood loss (mL)	50 (20-750)	58 (5-650)	0.568
Flatus (POD)	2 (1-3)	2 (1-5)	0.843
Food intake (POD)	3 (2-6)	3 (2-7)	0.598
Walking (POD)	2 (1-3)	1 (1-5)	0.073
Postoperative hospital stay (days)	12 (7-33)	12 (5-67)	0.907

Values are medians (range); POD: postoperative day.

TABLE 4 Post-operative Complications

	Previous surgery (n=21)	Control (n=100)	*p*-value
Wound infection	3 (14%)	11 (11%)	0.706
Anastomotic insufficiency	0	2 (2%)	0.518
Intra-abdominal abscess	0	1 (1%)	0.647
Ileus/bowel obstruction	0	3 (3%)	0.429
Death	0	0	N/A
Total number of patients	3 (14%)	15 (15%)*	0.945

*Two patients had multiple complications.

was defined as the completion of laparoscopy-assisted colorectal resection with an incision of 8cm or less in length for specimen extraction or the hand-assisted technique. The hand-assisted technique was used only in cases where abdominal adhesions or abdominal hemorrhages could not be handled by the regular laparoscopic technique. Initial access to the peritoneal cavity was achieved with the open technique at the umbilical region. In cases of a previous midline incision with a significant scar over the wound, the first access was created at a site away from the scar, also with the open technique. The StatView program version 5 (SAS Institute, Inc., Cary, North Carolina, USA) was used for all statistical analysis. The chi-square test was used to compare frequencies, and the Mann-Whitney U test was used to compare data between the 2 groups. The overall survival was calculated by the Kaplan-Meier method and analyzed by the log-rank test. $p<0.05$ was considered statistically significant.

RESULTS

During the study period, 471 patients underwent colorectal cancer resections for colorectal cancer in Shikoku Cancer Center. Among those patients, 121 patients (60 men and 61 women) underwent laparoscopic colectomy **(Table 1)**. The median age of the patients was 66 years (range: 37-93 years). For the 21 patients (17%) who had undergone 28 previous open abdominal surgeries, the types of surgery are shown in **Table 2**. No significant difference between the 2 groups was seen in the patients' demographics, the nature of their disease, and operation methods **(Table 1)**. In the peri-operative outcome analysis, the median operating time was 175 min (range: 75-330 min) in the previous surgery group, and was significantly longer than that in the control group (median: 155 min, range: 80-337) **(Table 3)**. However, blood loss, time to first flatus, time to food intake, time to walking, and postoperative hospital stay did not show any significant differences between the 2 groups. No conversion to open surgery was required in either group. Only 3 wound infections without major postoperative complications occurred in 3 patients (14%) in the previous surgery group, whereas the control group showed 17 complications in 15 patients (15%) that contained 2 cases of anastomotic insufficiencies **(Table 4)**. No patients died in the postoperative period. There was no significant difference in the postoperative complication incidence between the 2 groups. In the long-term outcome analysis, the median follow-up time was 84 months (range: 1-143). The 5-year overall survival rate for the previous surgery group and the control group

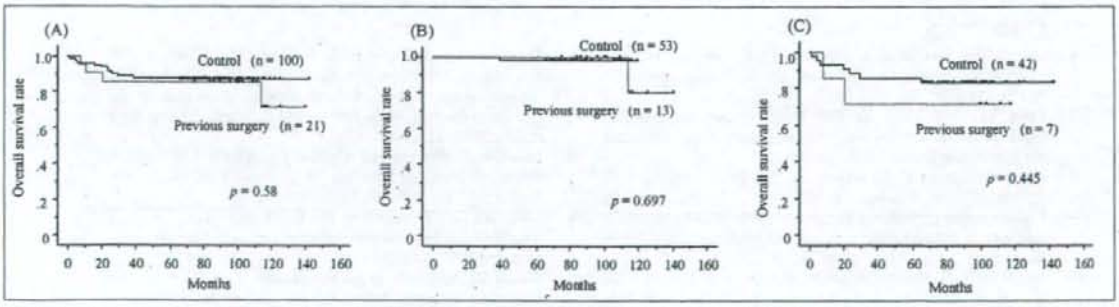

FIGURE 1 The overall survival in the previous surgery group *vs.* the control group by the Kaplan-Meier method. **(A)** All patients, **(B)** Duke's A patients, and **(C)** Duke's B & C patients showed no significant differences in the overall survival between the 2 groups by the log-rank test.

were 86% (n=21) and 88% (n=100) for all patients **(Figure 1A)**, 100% (n=13) and 98% (n=53) for Duke's A patients **(Figure 1B)**, and 71% (n=7) and 86% (n=42) for Duke's B and C combined patients **(Figure 1C)**, respectively, by the Kaplan-Meier method. No significant differences were observed in the overall survival between the 2 groups by the log-rank test.

DISCUSSION

This study was conducted to audit the peri-operative and long-term outcomes after laparoscopic colectomy for colorectal cancer patients with previous abdominal surgery. Previous abdominal surgery, which was once reported as a contraindication, is now becoming an indication for laparoscopic surgery (1-5). However there has been no known report that shows the long-term outcomes after laparoscopic colectomy for these patients. Needless to say, the minimally invasive surgery should not be the limited radical operation for cancer therapy. In this study, the minimally invasive surgery was shown to be consistent with its radical intent even for patients with previous surgery; there was no inferiority in the overall survival rate for patients with previous surgery when compared to the control group. In other words, given sufficient expertise, a large percentage of colon cancers can be managed laparoscopically with appropriate dissection and locoregional margins as well as in open surgery. The quality of the radical operation in this study was proven by the Kaplan-Meier survival data for 5-year overall survival: 98.5% for Duke's A (n=66), 84.6% for Duke's B (n=26), 82.6% for Duke's C (n=23), and 0% for Duke's D (n=6). These long-term outcomes for laparoscopic colorectal cancer surgery were acceptable and comparable with those of other institutes (6-8).

The median operating time in the previous surgery group (175 min, range: 75-330) was found to be significantly longer than that in the control group (155 min, range: 80-337). The dissection for adhesions due to previous surgery probably extended the operation time. Although too much prolongation in operation time may nullify the advantage of minimally invasive surgery, the 20 min extension in operation time seems acceptable. Moreover, the median operation times in this study were almost the same as other institutes (2,8-10).

In this study, we did not experience any conversion to open surgery in either group. This is probably because of careful judgment during patient selection and the use of the hand-assisted technique. For those cases which presented strong abdominal adhesions, advanced fixed tumors, or uncontrollable hemorrhages, a small incision (8cm or less) was made near the site in order to use the hand-assisted technique and those cases were managed safely. Moreover, the small incision could be used to look directly at the sites and manage them safely for those cases. There have been several reports that compared the hand-assisted laparoscopic and the standard laparoscopic colectomy (11,12). According to those reports, the extraction incision was longer in the hand-assisted group; however in this study the hand-assisted group showed that the operative time, postoperative complications, recovery and morbidity rates were similar in the 2 groups. Therefore, the hand-assisted technique may be considered a suitable and safe method for such cases, and not be regarded as a conversion if the extraction incision was 8cm or less in length.

The incidence of postoperative complications has been reported, in large laparoscopic series, to range from 6.8-38.3% (2,8-10,13,14) whereas this study had 20 postoperative complications in 18 patients (14.8%) which was similar to rates in other institutes. Although no significant differences were found in the incidences of postoperative complication between the 2 groups, it is remarkable that only 3 cases of wound infections without major complications were observed in the previous surgery group. It seems that the careful and meticulous surgical techniques and the use of the hand-assisted technique reduced the incidence of postoperative complications such as intra-abdominal abscesses or small bowel injuries.

In conclusion, with the exception of operation time, previous abdominal surgery did not yield significant differences in the peri-operative and long-term outcomes after laparoscopic colectomy for colorectal cancer patients. Consequently, previous abdominal surgery should not be regarded as a contraindication for laparoscopic colectomy if surgeons are careful in patient selection, and have safe and meticulous surgical techniques.

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ー腹腔鏡手術はどこまで適応されるかー

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はじめに

消化器外科領域における腹腔鏡下手術は，もはや胆嚢摘出術にとどまらず，ほとんどの腹部臓器に対して施行されているといっても過言ではない．なかでも1991年に端を発した腹腔鏡下大腸切除術laparoscopic-assisted colectomy（LAC）は，ここ10数年で急速に普及している．その理由は，大腸の血管走行が比較的単純なため腹腔鏡下での処理が容易であること，大腸壁が弾力性に富んでいるため，鉗子で把持しやすく剥離授動を行えば小切開創から体外へ挙上できることなどがあげられる．現時点では早期結腸癌がよい適応とされているが，今後さらに適応拡大が期待される術式である．

わが国における腹腔鏡下大腸切除術の変遷

日本内視鏡外科学会（JSES）が行った第8回アンケート調査によると[1]，2005年末までのわが国における小腸・大腸疾患に対する腹腔鏡下腸切除術総数は41,621件で，内訳は良性疾患14,803件，悪性疾患26,818件であった（図1）．悪性疾患のうちもっとも多いのが早期大腸癌で14,126例，ついで進行大腸癌12,411例，カルチノイド101例，肉腫41例，その他139例であった．早期癌と進行癌の割合は，1993年では早期癌が悪性疾患全体の90.3%を占めていたのに対し，進行癌はわずか8.9%であった．その後徐々に進行癌の割合が増加し，1998年では早期癌70.3%に対し，進行癌28.2%となり，2003年には両者はほぼ同数となり，2005年には両者は逆転し，早期癌41.2%に対し，進行癌57.6%までになった．それに伴ってリンパ節郭清もD3郭清の割合が増加しており，1998年にはD3郭清18.8%であったのに対し，2005年では40.0%まで増加した．施設別にみても進行癌に対してD3郭清を施行している施設が62%にまで達していることから，本

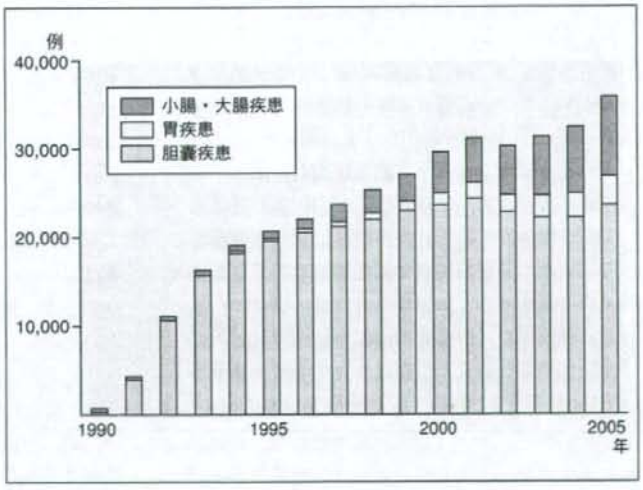

図1　腹部外科領域の疾患別症例数の推移
（文献1）より引用）

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- わが国における腹腔鏡下大腸切除術の総件数は年々増加している．
- 腹腔鏡下大腸切除術の利点はその低侵襲性と拡大視効果にある．
- 腹腔鏡下大腸切除術は現時点では早期結腸癌がよい適応である．

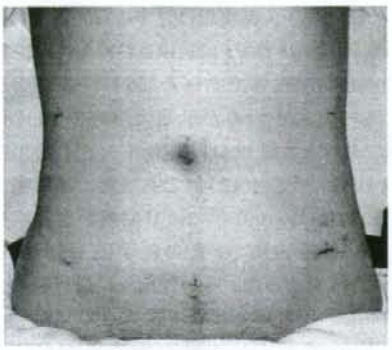

図2　腹腔鏡下低位前方切除術の創

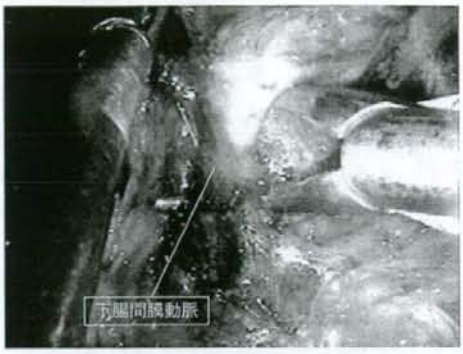

図3　腹腔鏡下でのリンパ節 D3 郭清

法が広く普及してきたことを示している．その反面，進行癌であっても D0～2 郭清にとどめている施設が 39% にのぼることから，進行癌に対する標準手術としては，まだ技術的に確立されていないともいえる．

腹腔鏡下大腸切除術の特徴と適応●

本法の最大の利点は，その低侵襲性にある．開腹大腸手術の平均的な術創が 20～30 cm ほどであるのに対し，腹腔鏡下手術では 2.5～8 cm 程度である(図 2)．小さな術創により得られる benefit はその整容性のみならず，術後疼痛の軽減や，早期離床といった点にも現れる．その結果，腸管蠕動も術後早期からみられ，早期経口摂取も可能となる．また，術後創感染や腸閉塞などの早期合併症発生率も少ないため術後在院日数の軽減につながり，最終的には医療費の削減が期待される．これまで各国で行われた結腸癌に対する腹腔鏡下手術と開腹手術を比較した大規模な randomized controlled trial (RCT)では，術中出血量，術後鎮痛薬の使用量，術後在院日数などの短期手術成績は腹腔鏡下手術群のほうが有意に優れているとの結果であった．またこれらの RCT の結果をレビューしたメタアナリシスでも同様の報告がされており[2]，腹腔鏡下手術の短期治療成績の有効性についてはほぼ確立されたといえる．

腹腔鏡のもつ拡大視効果は，より精緻なリンパ節郭清や自律神経温存手術を可能とした(図 3)．特に S 状結腸癌や直腸癌に対する腹腔鏡下手術では下腹神経叢や骨盤神経叢の視認性が向上したため，より確実な神経温存手術が可能になった．結果的にこれらの手術を多くの外科医が同時に画像として享受できるようになったことは，外科解剖の理解を深めることにつながったといえる．

一方，腹腔鏡下手術特有の問題点もある．まず手技的な面からは，テレビモニターに映し出される術野は二次元画像であるため，深部感覚を得にくいという点である．触感は常に鉗子を通して得られるため，血管やリンパ節の同定は視覚に頼らざるを得ない．特に縫合・止血操作は難易度が高いため，止血に難渋すると開腹手術への移行を余儀なくされる．また，助手は術者と反対側に立ち，

- 腹腔鏡下大腸切除術の難易度は技術の習熟により解決しうる問題である.
- 腹腔鏡下直腸切離の手技向上・器具改良が縫合不全回避のポイントである.
- 欧米からの報告では開腹手術と腹腔鏡下大腸切除術の再発率に差はない.

別のモニターを見ながらの介助となるため，左右逆の動きとなる「ミラーイメージ」での手技になることや，細部の観察が可能になった反面，術野が狭くなるため全体像を把握しにくいという点などから，他臓器損傷などの副損傷も危惧される．したがって術者のみならずチーム全体での技術の習熟が要求される．また，直腸癌では，狭い骨盤腔で良好な視野を展開するために，さらに高度な技術と器具が必要となる．特に，腫瘍の肛門側腸管を切離する際の自動縫合器の選択と使用法は，術後縫合不全を回避するための重要なポイントである．現時点での縫合不全は5～10%程度に認められ，手技の向上のみならず，より安全で使いやすい器具の改良・開発も急務である．

癌治療の観点から述べると，第一に視診・触診による検索ができないため，術中診断を視覚に頼らざるをえないという点があげられる．つまり，術野から離れた部位にあるリンパ節の腫脹や腹腔内他臓器転移，腹膜播種を見逃す可能性があるということである．第二に，炭酸ガスが与える癌細胞の生物学的悪性度への影響も懸念される．しかし炭酸ガスが癌細胞の接着を促進し，その結果肝転移が促進されたという実験報告はあるが[3]，これまでの臨床例での検討において，実験結果を支持するような報告はない．第三に，リンパ節郭清度の低下の点である．たしかに主幹動脈の根部を露出するD3郭清では，高度な技術が要求される．しかし各国のRCTの結果によれば開腹手術と比較して，郭清したリンパ節の個数には差はないと報告されていることから[4]，技術の向上により打開できる問題であろう．最も問題視されてきたのが，腹腔鏡手術後のポート部再発port site recurrence (PSR)である．PSRは1990年代なかばに欧米で相ついで報告され，わが国でも腹腔鏡下手術後再発が懸念された．しかし，実際のPSR発生率は1%未満であり，これは開腹手術後の創部再発とほぼ同等であることから，現在では腹腔鏡下手術特有の再発形式ではないと理解されている．

近年，英国のConventional versus Laparoscopic-Assisted Surgery in Colorectal Cancer (CLASICC) Trial Groupから結腸直腸癌の中期治療成績が報告された[5]．それによれば，術後3年の時点での無再発率(DFS)，全生存率(OS)は開腹手術群と腹腔鏡下手術群に差はなく，局所再発率や遠隔再発率も同等であった．また米国のClinical Outcomes of Surgical Therapy (COST) Study Groupからは，さらにstage I～IIIいずれにおいても5年生存率(OS)は両群間に差はないと報告され[6]，現時点では腹腔鏡下手術の治療成績は少なくとも開腹手術に劣らないといえる．しかし，わが国の大腸癌治療ガイドライン2005年度版によれば，腹腔鏡下大腸切除術は結腸および直腸S状部癌のstage 0～Iに対してのみ推奨されており，stage II，IIIの進行癌に対する腹腔鏡下手術の意義は現在進行中のRCT (JCOG0404)の成績を見て判断されるべきであろう．また，腫瘍下縁が腹膜翻転部より肛門側にありかつ直腸壁を貫通している直腸癌の側方リンパ節転移率は20.1%であり，このような症例に対して側方郭清を行った場合，骨盤内再発の危険性をおよそ50%減少させることができ，また5年生存率も9%向上すると予測されている．したがってT3以深の下部直腸癌に対する側方郭清はわが国では標準的手術と認められている．現在の腹腔鏡下手術では，開腹手術と同等の側方郭清ができるとは限らない．少なくともT3以深の下部直腸癌に対する腹腔鏡下手術の適応は考慮すべきである．T1～2直腸癌の腹腔鏡下手術の治療成績は，経口摂取開始や術後在院日数など短期治療成績は開

- わが国での進行結腸癌に対する腹腔鏡手術と開腹手術の RCT は現在進行中である.
- 欧米では T1～2 直腸癌に対する腹腔鏡手術は低侵襲手術と結論づけられた.
- 進行下部直腸癌に対する腹腔鏡手術は，まだ標準的治療とはいえない.

腹手術より優れているとの報告がある．これらをまとめたメタアナリシスでも，腹腔鏡下直腸切除術は低侵襲手術と結論づけられた[7]．また，術後再発率や生存率にも差はないとの報告もある．しかし，縫合不全率は開腹手術群 6.7% に対して腹腔鏡下手術群では 8.4% (p＝0.76) と有意差はないものの腹腔鏡下手術群で高い傾向にあり，安全な標準的治療としての評価を得るためには，直腸の切離・吻合といった問題を解決していく必要がある．また，わが国で施行した RCT による評価も今後必要であろう．

おわりに

わが国で LAC が導入されてから 15 年が経過した．この間に，適応の拡大，手技の工夫を繰り返しながら現在の手法にほぼ定着した．一方，縫合不全や術後再発の問題など，解決すべき問題も残っている．また，進行結腸癌や直腸癌に対する適応の可否については，今後の研究成果に注目したい．

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Preoperative Serum Carcinoembryonic Antigen Level as a Predictive Factor of Recurrence After Curative Resection of Colorectal Cancer

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Background: We evaluated the prognostic value of the preoperative serum carcinoembryonic antigen (CEA) level in patients with colorectal cancer (CRC).

Patients and Methods: The study group comprised 638 patients. The optimal cutoff value for the preoperative serum CEA level was determined. Predictive factors of recurrence were evaluated using multivariate analyses. The relapse-free time was investigated according to the CEA level.

Results: All patients underwent potentially curative resection for CRC without distant metastasis, classified as stage I, II, or III. The optimal cutoff value for preoperative serum CEA level was 10 ng/ml. Elevated preoperative serum CEA level was observed in 92 patients. Multivariate analysis identified tumor–node–metastasis (TNM) stage and preoperative serum CEA level as independent predictive factors of recurrence. The relapse-free survival between CEA levels >10 ng/ml and <10 ng/ml significantly differed in patients with stage II and III. However, there was no significant difference in relapse-free survival between CEA levels >10 ng/ml and <10 ng/ml in patients with stage I.

Conclusion: Preoperative serum CEA is a reliable predictive factor of recurrence after curative surgery in CRC patients and a useful indicator of the optimal treatment after resection, particularly for cases classified as stage II or stage III.

Colorectal cancer (CRC) is a common malignancy and the second commonest cause of cancer-related death in Japan; it was estimated that >92,000 new cases of CRC occurred in the year 2000 and that >40,000 people died of the disease in 2004.[1] The Japanese Society for Cancer of the Colon and Rectum reported 5-year survival rates, in 2004, of 94.3%, 90.6%, 81.2%, 71.4%, 56.0%, and 13.2%, respectively, for cases classified as stage 0, I, II, IIIa, IIIb, and IV based on the *Japanese General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum, and Anus*.[2] To further improve survival rates, it is important to identify predictive factors for relapse. Based on the predictive factors, it may be possible to improve survival by some treatments.

The International Union against Cancer (UICC) tumor–node–metastasis (TNM) classification is recognized as the best predictor of outcome, and precise

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staging is necessary to treat CRC. No residual tumor should be left if CRC is diagnosed as capable of potentially curative resection. Advances in chemotherapy for CRC have led to the development of several regimens to prevent relapse. Since the early 1990s, adjuvant chemotherapy with a 5-fluorouracil (5-FU) plus leucovorin (LV) regimen has been recognized as standard therapy for patients with UICC stage III colon cancer, and has resulted in a 30% decrease in the relapse rates compared with surgery alone.[3–6] Recently, the addition of oxaliplatin to the 5-FU/LV therapy regimen (the MOSAIC regimen) or the capecitabine regimen has further improved patient outcomes, and these approaches are being accepted as a new standard of care.[7,8] In cases of recurrence after colorectal surgery, several reports have indicated that a 5-FU-based regimen with the addition of oxaliplatin (FOLFOX) or irinotecan (FOLFIRI), or monoclonal antibodies such as cetuximab and bevacizumab, can improve patient outcome.[9–11] Thus, identification of predictive factors for recurrence and early detection of relapse are crucial to improve CRC treatment.

Several reports have suggested that the postoperative serum CEA level is a useful marker of recurrence after colorectal surgery.[12–15] Moreover, it can be measured cheaply and easily. Monitoring of the postoperative CEA level is thus commonly used in the follow-up of CRC patients.[15–19] However, there has been some controversy about the significance of the preoperative CEA level as a predictive factor of recurrence.[20–22] Furthermore, few previous reports have considered optimal cutoff values for CEA levels.[23,24]

The current study evaluated the optimal cutoff value for the CEA level in patients with CRC, and its efficacy as a predictive factor of recurrence.

PATIENTS AND METHODS

Between April 1992 and February 2003, 816 patients underwent colorectal surgery at the Gastroenterological Centre of Yokohama City University Medical Centre, Japan. Of these, a series of 638 patients with stage I, II, and III received potentially curative colorectal surgery. Curative resection was defined by the absence of any gross residual tumor from the surgical bed and a surgical resection margin that was pathologically negative for tumor invasion. One hundred seventy-eight patients were excluded from the present study because of stage IV (n = 150) and noncurative resection (n = 28). Data were retrieved from operative and pathological reports. Follow-up data were obtained from the outpatient clinical database.

The study group comprised 380 men and 258 women aged 26–92 years (median and quartiles 64 and 57–71 years, respectively). Patients with macroscopic peritoneal metastasis, positive peritoneal lavage cytology, unresectable bulky tumor, or distant metastasis were excluded from the study. Of these 638 patients, 169 were subsequently classified as stage I, 221 as stage II, and 248 as stage III. After 1997, 185 patients with good performance status who gave informed consent received adjuvant chemotherapies. Starting 12 weeks after curative surgery, pyrimidine-fluoride-based regimens were mainly used for 1–2 years in patients classified as stage III.

Preoperative imaging studies were routinely performed following a barium enema and colorectal fiber examination, using abdominal ultrasonography (US) and computed tomography (CT) to determine the location, macroscopic appearance, diameter, and depth of invasion of the tumor, as well as lymph node metastasis and distant metastasis.

Staging was principally based on the UICC/TNM classification of CRC. Experienced pathologists from our institution participated in this study and maintained the quality of the diagnosis. Of the 638 registered patients, 336 had tumors located in the colon and 302 had tumors located in the rectum. The pathologic tumor diameter indicated the maximum microscopic length of the tumor irrespective of the depth. Differentiated tumors were histologically observed in 578 patients, and undifferentiated tumors were seen in 60 patients. Lymphatic invasion was observed in 273 patients, and vascular invasion was observed in 362 patients.

All patients were followed up every 12–16 weeks for at least 5 years according to our standard protocol, which included tumor-marker studies, CT, colorectal fiber examinations, US, and chest radiography. Bone scans were performed when bone metastasis was indicated. The development of new or recurrent metastatic lesions following surgery was defined as a postoperative relapse. Median follow-up time was 78.9 ± 38.5 months for all registered patients. The study was retrospective and neither randomized nor controlled.

Detection of Serum CEA

Serum CEA was measured preoperatively by an Elecsys CEA electrochemiluminescence assay on a Modular Analytics E170 system (Roche Diagnostics

K.K, Tokyo, Japan). The normal range for serum CEA is 0–4.9 ng/ml at our institution.

Statistical Analysis

All data were analyzed using SPSS software version 10.0 for Windows (SPSS Inc., Chicago, IL). The clinical endpoint of this study was overall relapse-free survival. Relapse-free survival was calculated using the Kaplan–Meier estimation method and examined by the log-rank test. The chi-square test was used to evaluate the differences in proportions and the Student's *t*-test was used to evaluate the continuous variables. All data were expressed as the mean ± standard deviation SD. A multivariate analysis using a stepwise forward Cox proportional hazards regression procedure was performed for relapse-free survival. In this analysis, nine variables were employed as follows: age, sex, tumor location, tumor diameter, histological type, lymphatic invasion, hematological invasion, preoperative CEA level, and TNM stage. Probability (*P*) values were considered statistically significant at the 0.05 level. The clinicopathological terminology principally followed the UICC/TNM classification.

RESULTS

Stratification of Preoperative Serum CEA Level

To confirm the optimal classification of the serum CEA level, time to relapse was calculated at 5 ng/ml intervals. The relapse-free survival was compared between the groups with lower and higher CEA levels at each threshold. Multivariate Cox proportional hazards regression was used to compare the time to relapse between the two groups. The preoperative serum CEA level with the highest chi-square value was regarded as the optimal critical point of classification. The most significant difference in relapse-free survival was detected at a threshold value of 10 ng/ml [$\chi^2 = 35.310$, hazard ratio (95% confidence interval) = 3.210 (2.185–4.715), $P < 0.0001$; Table 1]. The critical cutoff value of the CEA level was thus defined as 10 ng/ml.

Comparison of Clinicopathological Factors Between Patients with CEA Levels <10 ng/ml and >10 ng/ml

There were significant differences in tumor diameter, lymphatic invasion, and TNM stage between the two groups. The high CEA patients tended to have a larger tumor diameter, higher incidence of lymphatic invasion, and more advanced TNM stage (Table 2). There was no significant difference in the application of adjuvant chemotherapies between the two groups.

TABLE 1. *χ^2 values and hazard ratios according to serum CEA levels calculated by the Cox proportional regression hazard model*

Threshold (ng/ml)	χ^2	Hazard ratio (95% CI)	*P* value
<5, ≥5	27.505	2.631 (1.833–3.776)	<0.001
<10, ≥10	35.310	3.210 (2.185–4.715)	<0.001
<15, ≥15	30.941	3.201 (2.137–4.884)	<0.001
<20, ≥20	18.670	2.882 (1.783–4.657)	<0.001
<25, ≥25	18.379	3.073 (1.839–5.134)	<0.001
<30, ≥30	16.738	3.203 (1.834–5.594)	<0.001
<40, ≥40	4.314	2.138 (1.044–4.381)	0.038

CI, confidence interval.

TABLE 2. *Patient characteristics according to serum CEA levels*

Variables	CEA (<10 ng/ml) (*n* = 546)	CEA (≥10 ng/ml) (*n* = 92)	*P* value
Age (years)			
<75/≥75	473/73	79/13	0.843
Sex			
Male/female	321/225	59/33	0.334
Tumor diameter (cm)			
<5/≥5	344/202	32/60	<0.001
Location			
Colon/rectum	297/249	45/47	0.381
Histologic type			0.365
Differentiated	497	81	
Undifferentiated	49	11	
Lymphatic invasion			
Absence/presence	243/303	30/62	0.031
Vascular invasion			
Absence/presence	317/229	45/47	0.101
UICC/TNM staging			
I/II/III	163/185/198	6/36/50	<0.001
Curability			
R0/R1	533/13	87/5	0.102
Recurrence			
Absence/presence	462/84	54/38	<0.001

Comparison of Relapse-Free Survival According to Stage and Pattern of Recurrence Between Patients with CEA <10 ng/ml and >10 ng/ml

Overall, there were significant differences in relapse-free survival between the two groups (Fig. 1). There was no significant difference in relapse-free survival among patients classified as stage I (Fig. 2). However, there were significant differences among those classified as stage II and stage III ($P = 0.036$ and $P < 0.001$, respectively; Figs. 3 and 4). Recurrence was observed in 38 (41.3%) patients with CEA

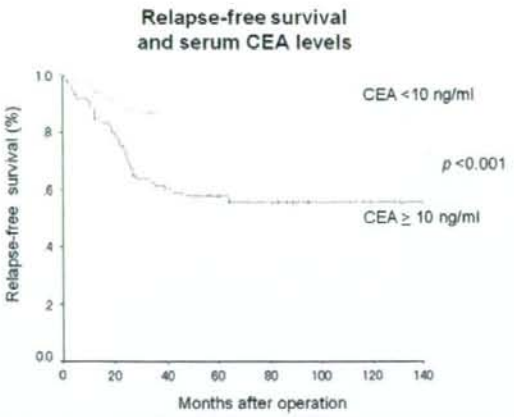

FIG. 1. Relapse-free survival and serum CEA levels. Comparison of relapse-free survival according to serum CEA level.

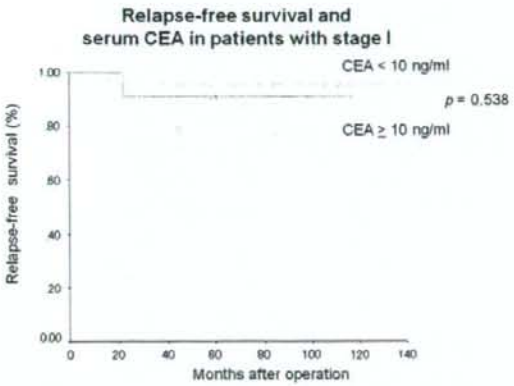

FIG. 2. Relapse-free survival and serum CEA in patients with stage I.

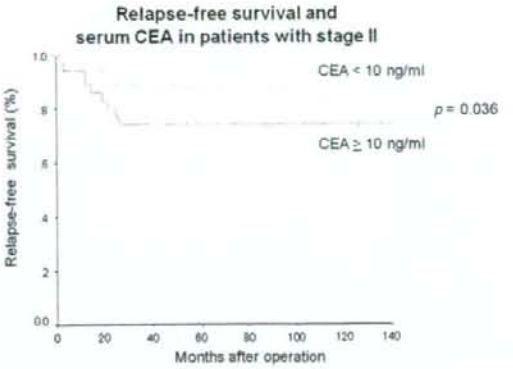

FIG. 3. Relapse-free survival and serum CEA in patients with stage II.

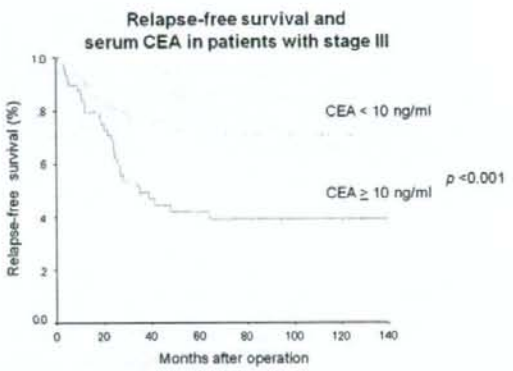

FIG. 4. Relapse-free survival and serum CEA in patients with stage III.

>10 ng/ml and in 84 (15.4%) patients with CEA <10 ng/ml ($P < 0.001$). However, there was no significant difference in the pattern of recurrence between the two groups. The local recurrence rates were 23.7% for CEA >10 ng/ml and 14.3% for CEA <10 ng/ml. The distant metastasis rates were 76.3% and 84.5%, respectively (Table 3).

Prognostic Factors for Relapse-Free Survival

The multivariate analysis showed that preoperative serum CEA level and TNM stage independently affected relapse-free survival. However, age, sex, tumor location, tumor diameter, lymphatic invasion, vascular invasion, and microscopic appearance were not independent prognostic factors on multivariate analysis (Table 4).

DISCUSSION

Serum CEA was originally reported in 1965 by Gold and Freedman.[22] This factor is cheap and easy to measure, and postoperative CEA is commonly assessed in the follow-up of CRC patients.[15,17–20] However, there has been controversy about the significance of the preoperative CEA level as a predictive factor of recurrence,[20–22] and only a few reports have evaluated optimal cutoff values.[23,24] Some previous reports have defined 5 ng/ml as the cutoff value for

TABLE 3. *Prognostic factors for relapse-free survival*

	Multivariate Cox regression result	
Variable	Hazard ratios (95% CI)	*P* value
Serum CEA level (ng/ml)		
<10/≥10	3.064 (1.839–5.105)	<0.001
UICC/TNM staging		
II/I	6.210 (1.281–7.924)	0.013
III/I	7.225 (3.792–21.584)	<0.001

CI, confidence interval.

TABLE 4. *Patterns of recurrence according to preoperative serum CEA levels*

			$n = 122$
	CEA (<10 ng/ml) ($n = 84$)	CEA (≥10 ng/ml) ($n = 38$)	*P* value
			0.214
Local recurrence	12 (14.3%)	9 (23.7%)	
Anastomotic	2	2	
Pelvic or tumor bed	6	4	
Nodal	4	3	
Distant metastasis	71 (84.5%)	29 (76.3%)	
Hepatic	41	11	
Pulmonary	35	17	
Peritoneal	8	2	
Osseous	7	2	
Brain	5	3	

One patient had an unknown recurrence pattern.

the CEA level.[16,25–27] However, applying this cutoff value selects too many patients (approximately 25%) as high risk (in the current report, 24.6% of patients had CEA >5 ng/ml). Moreover, in our study, the most significant difference in relapse-free survival was detected at a threshold value of 10 ng/ml. However, it is necessary to validation of the optimal threshold in an independent patient group. In the current study, 14.4% of patients had CEA level >10 ng/ml. Moreover, when we limited the analysis to patients with CEA >5 ng/ml, the optimal cutoff value as a predictive factor for relapse was also 10 ng/ml (data not shown). These results confirm that a cutoff value of 10 ng/ml is a more powerful prognostic factor for recurrence than the usual value of 5 ng/ml.

Even after potentially curative resection, patients with CEA > 10 ng/ml showed a high rate of recurrence (41.3%) compared with patients with CEA < 10 ng/ml (15.4%). However, there was no significant difference in relapse-free survival among patients classified as stage I. This might have resulted from the relatively small number of patients with high CEA levels among those classified as stage I ($n = 6$). However, this result suggested that patients classified as stage I could only be treated surgically.

Patients classified as having high and low preoperative CEA levels showed significant differences in relapse-free survival in stages II and III. These findings suggested that the patients with high CEA levels might have harbored undetectable distant metastatic disease around the time of the operation. Julia et al. reported that, of stage I or II patients, 32.8% tested positive for disseminated tumor cells after surgery, and patients who were marker-positive for disseminated cells in post-resection lavage samples showed significantly poorer prognosis.[28] These results suggested that, even though curative resection was performed, residual tumor cells were present. Furthermore, Sadahiro et al. reported that the presence of CEA messenger RNA-expressing cells in peripheral blood 7 days after curative surgery was a novel independent factor predicting recurrence in patients with CRC.[29] These reports suggested that conventional staging alone was not suitable for the postoperative treatment of such patients.

Although relapse-free survival was compared according to the preoperative serum level of CEA in this study, it is also important to compare disease-specific and overall survivals in these patients. Disease-specific survival and overall survival significantly differed between patients with CEA < 10 ng/ml and CEA > 10 ng/ml (5-year survival, 90.7% versus 77.2%, $P = 0.002$; 84.8% versus 72.2%, $P = 0.005$, respectively).

In the current study, 547 patients had CEA <10 ng/ml and 81 patients relapsed. We investigated the predictive factors of recurrence in these patients. Multivariate analysis showed that only TNM stage was a significant factor ($P < 0.001$), while lymphatic invasion tended to be a predictive factor for recurrence ($P = 0.061$ and data not shown). There was no difference in recurrence pattern between the two groups. Multivariate analysis identified the TNM stage and the preoperative CEA level as predictive factors for relapse. Previously, several reports suggested that preoperative CEA was a significant prognostic factor only in patients classified as stage II or stage III.[5,16,27] Park and Lee also mentioned the CEA level of 10 ng/ml as the cutoff value to predict recurrence in Dukes' C rectal cancer patients. They concluded that adjuvant therapy should be administered in patients with elevated preoperative serum CEA level.[30] Our results support their findings.

In 1993, the National Surgical Adjuvant Breast and Bowel Project (NSABP) reported the results of a surgical adjuvant clinical trail that indicated signifi-

cant prolongation of both disease-free survival and overall survival in stage II and III colon cancer patients who received FU plus LV compared with patients who received semustine, vincristine, and FU.[5] Following on from this work, there have been several studies comparing the efficacy of different regimens for adjuvant chemotherapy after curative resection of CRC. Recently, the European MOSAIC trial reported the efficacy of infused 5-FU, leucovorin, and oxaliplatin (FOLFOX4) compared with 5-FU/LV in an adjuvant setting in 2,246 patients with completely resected stage II and III colon cancer.[7] Based on the results, FOLFOX4 has been recommended as a treatment for early-stage colon cancer in the National Comprehensive Cancer Network (NCCN) guidelines.

However, even though these chemotherapies have been shown to be effective, they remain costly. There have been several reported economic analyses of adjuvant chemotherapy for CRC.[31–33] Adjuvant chemotherapy has been accepted as the standard treatment for stage III CRC. However, adjuvant chemotherapy for stage II CRC remains controversial and is not routinely recommended to all patients. According to the current American Society of Clinical Oncology guidelines, the criteria used to indicate adjuvant chemotherapy are poorly differentiated histology, T4 lesions, bowel perforation, and inadequate number of sampled lymph nodes (<13).

It is important to identify patients who are at high risk of relapse, especially in stage II. Our study suggests that a cutoff value for preoperative CEA of 10 ng/ml is a powerful marker of postoperative relapse. In patients with a high CEA level, adjuvant chemotherapy such as FOLFOX4 should also be recommended.

The introduction of chemotherapy for recurrence caused clinical bias when the outcome measure was overall survival time; we therefore used disease-free survival time as the outcome in the current study. After 1997, 185 patients receiving adjuvant chemotherapy were included in the study; however, we detected no significant difference due to the use of adjuvant chemotherapy based on the preoperative CEA levels. By restricting the outcome to disease-free survival time, this report provided additional evidence that the preoperative CEA level is a useful marker.

This study included relatively older patients for a long duration. Therefore, a further study of high-volume patients will be necessary to identify the optimal classification for preoperative CEA level in CRC.

In conclusion, the preoperative serum CEA level in patients with CRC, which can be measured easily prior to surgery, is a reliable predictive factor of recurrence. This measure might therefore be a candidate for use in the staging system, in addition to conventional factors such as lymph node metastasis or depth of invasion, and will be useful for treatment planning in patients undergoing curative resection of CRC, especially those classified as stage II or III.

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直腸癌の手術

Navigation surgery for rectal cancer

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●要旨●直腸癌の手術は初発，再発ともに術式に多くの選択肢があり，画像診断による術前シミュレーションが重要である。壁深達度，他臓器浸潤の範囲を十分に診断したうえで，局所切除かリンパ節郭清を伴う標準手術か，あるいは周辺臓器の合併切除，側方リンパ節郭清を行うか否かの選択をすることになる。局所再発の診断能はPET-CTが優れている。骨盤腔の実体モデルを作成して三次元的にシミュレーションすることも有用である。さまざまなmodalityを用いて，生命予後向上とQOL維持のバランスをとりながら術式選択を行う必要がある。

● key words：PET-CT，局所再発，膀胱浸潤，術前シミュレーション，実体モデル

はじめに

直腸癌の手術は，骨盤腔という狭く奥行きのある三次元的な構造の中で，重要な神経や血管を温存しつつ行う必要があり，画像ナビゲーションの果たす役割は大きい。とくに，最近の腹腔鏡下手術の普及により，従来術者の触覚に頼っていた部分でも画像ナビゲーションが必要となってきた。また，局所再発の手術では，膀胱や仙骨への浸潤の程度によって術式が大きく変わる。

本稿では，再発を含めた直腸癌の術式選択のために有用となる画像ナビゲーションについて，われわれの取り組みを含めて紹介する。画像ナビゲーションは，いわゆる"Navigation Surgery"[1]という言葉に表されるように，本来術中に行われるものであるが，現実的には詳細な術前シミュレーションと一体をなすものである。本稿では，術前シミュレーションと画像ナビゲーションをとくに区別せずに取り扱っていく。

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初発直腸癌の手術

1. 血管3D再構築によるナビゲーション

直腸癌の場合は，右側結腸と異なり，主幹動静脈の走行にバリエーションが少ない。しかしながら，左結腸動脈（LCA）が下腸間膜動脈（IMA）根部からどれくらいの距離で分岐するか，あるいはS状結腸動脈第1枝と共通幹を形成するかという情報は術前に得ておく必要がある。これは腹腔鏡下手術の場合にとくに有用である（図1，2）。

2. 術前点墨とクリッピング

腹腔鏡下大腸癌手術の場合，触診による腫瘍の部位診断が困難であるため，点墨が必要とされている。点墨の量は0.1～0.2mlとごく少ない量を正確に粘膜下に注入することが望ましい。しかしながら，実際には多く注入されることがよくある。直腸癌の場合，墨が筋層にまで過量に注入されることにより，正確な剝離操作に支障をきたすこともある。また，吻合したい部分に墨が拡散しているために予定より肛門側で吻合せざるを得ないことにもなりかねない。

したがって，直腸癌では原則として点墨を行っていない。どうしてもわからない場合は肛門から入れた指

図1　血管3D画像－1
下腸間膜動脈（IMA）から左結腸動脈（LCA）が単独で分枝しているタイプ

図2　血管3D画像－2
下腸間膜動脈（IMA）から左結腸動脈（LCA）とS状結腸動脈第1枝（S-1），
上直腸動脈（SRA）がほぼ同レベルで分枝しているタイプ

で確認するか，術中内視鏡を行って腫瘍の位置を確認するようにしている。

なお，ごく微小な病変や，EMR後の追加切除のように，指でも腫瘍を確認できない場合は，病変の肛門側に内視鏡下にマーキングクリップを打ち，肛門から入れた指でクリップを触知しながら切離線を決めるようにしている。

3. 局在診断

従来，直腸癌の粘膜面での腫瘍下縁と切離線との距

離は2cm必要で，肛門管上縁までの距離が2cm以下の癌では直腸切断術とされてきた。ところが，最近の研究から，危険因子がなければこの距離は1cmでよく，後述する壁深達度の条件を満たせば，内括約筋の部分的または全摘除による括約筋間切除（ISR）の適応となることもある[8]。

局在診断には，注腸，CTおよびMRIのsagittal viewが用いられる。直腸指診の際に肛門を締めてもらうのも，画像とはいえないが，外括約筋と腫瘍の位置を知るうえで大切な検査である。

4. 壁深達度診断

1) 早期癌の場合（EUS, MRI, CT, endorectal coil MRI）

内視鏡的粘膜切除（EMR）か，外科的局所切除（TEM）か，あるいは根治手術かについては，患者のQOLを大きく左右する大変重要な問題である。深達度が，MかSMか，あるいはMPかを正確に診断する必要がある。MまたはSMの1000μm以下の浸潤であれば，EMRまたはTEMなどの局所切除でよいとされている。

欧米では経肛門的超音波診断（endorectal ultrasound）や経内視鏡的超音波（endoscopic ultrasound）がよく行われているが，日本ではすべての施設で行われているわけではない。正診率が高いとする報告もあるが，験者の技量によるところが大きい[9]。同様にendorectal MRIもまだ使用できる施設は少ない。拡大内視鏡によるpit patternやNBI画像による深達度診断も一般病院では普及しているとは言い難い。結局，肉眼所見や触診といった主観的な基準で術前診断が行われていることが多いのが実情である。

近年，ESDやTEMの技術が進歩し，腫瘍径についてはかなり大きなものも局所切除可能になっている。患者のQOLを考慮する意味からも，まずtotal biopsyという意味で腫瘍を切除し，詳細な病理組織学的検討を行い，追加切除や追加化学療法を検討するという考え方もある。いずれにしても，直腸の早期癌については，今後さまざまなmodalityによる術前診断の精度向上が進んでいくと予想される。

2) 進行癌の場合

Rbの癌で経腹的な吻合が困難な場合，括約筋間切除が行われている。適応は施設により若干異なるが，深達度MPまでとしていることが多い。外括約筋を一部切除した場合の排便機能については，未知の部分が多く，満足な結果が得られないとする報告もあるからである。

また，『大腸癌治療ガイドライン』によれば，現在，原則的に直腸癌（RaおよびRb）の治療に腹腔鏡下手術は適応されない。しかしながら，一部の施設ではStage Iの直腸癌に腹腔鏡下手術が行われている。現在進行中の多施設共同第II相試験も，Stage Iを対象としている。

これらの状況下では，進行直腸癌の深達度診断，すなわちMPかAかが術式決定に関わってくる。現在，MPまたはAの進行直腸癌の術前深達度診断は，MD-CT，MRI，注腸所見および直腸指診の所見から総合的に判断されている。これらに加えて腫瘍粘膜下生検の所見を参考にしている報告もある[10]。

3) 他臓器浸潤が疑われる場合

さらに深い進行癌では，膀胱や前立腺，子宮，膣といった隣接臓器への浸潤の有無が術式決定に関わってくる。直腸癌の場合，他臓器浸潤は局所の炎症を伴うことが多く，画像診断で炎症と癌の浸潤を区別することは困難である。また，たとえ病理組織にて明らかな癌の浸潤はなくても，微細な癌細胞が遺残していることもある。

さらに，直腸癌の局所再発は以後の治療が難しく，QOLをよけいに損なうことになりかねないため，「疑わしい場合は合併切除する」という方針を基本にすべきである。とはいうものの，術前診断を詳細に行うことは重要であり，術前にいくつかの可能性を想定してシミュレーションしておく必要がある。以下に，術前カンファレンスでの診断と病理結果が異なっていた症例をあえて提示する。

症例1：術前診断にて膀胱浸潤を疑ったが実際には浸潤のなかった症例

RS癌の女性（図3）。術前のMD-CTおよびMRにて腫瘍の膀胱浸潤が疑われた。手術中の触診でも浸潤を確信し，膀胱合併切除（回腸導管による尿路変更）を行った。病理組織検査の結果，浸潤は認められなかった。

このようなケースにはよく遭遇する。結果的に浸潤がないからといって，膀胱との剝離面を保つことは困難であり，術前の放射線科，消化器内科との合同カンファレンスの結果を尊重しつつ，手術を進めるべきである。

症例2：術前診断にて膀胱浸潤なしと診断されたが実際には浸潤のあった症例