randomized controlled trials comparing laparoscopic with conventional open surgery have been published, demonstrating that laparoscopic surgery for colon cancer was equivalent to open surgery in terms of postoperative complications and long-term outcome [4, 11, 18]. After the publication of these trials, laparoscopic surgery for colon cancer has been recognized as an alternative treatment to open surgery.

However, these studies did not include rectal cancer because of technical difficulties including anastomotic techniques, except the Conventional versus Laparoscopic-Assisted Surgery in Patients with Colorectal Cancer (CLASICC) trial, which included rectal cancer and showed impaired short-term outcomes in patients undergoing laparoscopic anterior resection for rectal cancer, and concluded that the routine use of laparoscopy for rectal cancer is not justified. There are some reports about the feasibility of laparoscopic surgery for rectal cancer, however, these studies included only a small number of patients, and the role of laparoscopy for rectal cancer remains to be defined [1, 2, 19, 22, 24].

This retrospective, multicenter study was conducted to clarify the feasibility, safety, and short-term and mid-term surgical outcomes of laparoscopic surgery for rectal cancer. To the best of our knowledge, the present study is the first retrospective study that included the data of more than 1,000 patients with rectal cancer undergoing laparoscopic surgery.

Patients and methods

This multicenter study was conducted by 28 institutions which are members of the Japan Society of Laparoscopic Colorectal Surgery. The study group consisted of patients who underwent laparoscopic surgery for rectal cancer in those 28 institutions during the period between May 1994 and February 2006. All of the surgeons were skillful both in the open and laparoscopic colorectal surgery, and had experienced at least 30 laparoscopic surgeries for colorectal cancer.

Indications for laparoscopic surgery for colorectal cancer have expanded gradually throughout Japan, based on the preoperative diagnosis of the tumor. Therefore, the indications for laparoscopic surgery for rectal cancer varied amongst the institutions, and the patients were selected at the surgeons' discretion. In the majority of institutions, indications were limited to T1 or T2 tumors in the rectum, and patients with bulky tumors, those with a previous history of extensive adhesions, those with bowel obstruction, and those who did not consent to laparoscopic surgery were excluded. No hand-assisted laparoscopic procedures were included in the present study.

Tumor location was defined according to the *General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum, and Anus* edited by the Japanese Society for Cancer of the Colon and Rectum [16]. When the tumor was located between the inferior margin of the second sacral vertebra and the peritoneal reflection, the location was recorded as the upper rectum. When the tumor was located below the peritoneal reflection, its location was recorded as the lower rectum. The location of the tumor was determined by pelvic computed tomography (CT) scan, colonoscopy, and/or barium enema preoperatively and confirmed during surgery.

The extent of lymphadenectomy and site of ligation and division of the inferior mesenteric vessels were decided by the surgeon in charge. Conversion to open surgery was defined as incision longer than 8 cm. In laparoscopic low anterior resection, the rectum was transected laparoscopically using laparoscopic linear staplers or through a small laparotomy, at the surgeon's discretion. A diverting stoma was also fashioned at the surgeon's discretion.

Clinical data including sex, age, body mass index (BMI), tumor location from anal verge, location of the tumor, laparoscopic procedures, size of tumor, distal margin, lymph node resected, and pTNM stage were collected retrospectively and reviewed. Operative and postoperative data including operative time, blood loss, length of incision, intraoperative complications, reasons for conversion to open surgery, time until resumption of liquid and solid intake, length of postoperative hospital stay, morbidity, 30-day mortality, and reason for reoperation were also collected retrospectively, and data regarding oncologic follow-up were collected at the time of the present study.

Statistical differences in categorical variables were analyzed by the chi-square test, and differences in continuous variables were analyzed by Student's *t*-test. The Kaplan–Meier method was used to calculate survival rates.

Results

Between May 1994 and February 2006, 1057 patients with rectal cancer underwent laparoscopic surgery. The patient details are summarized in Table 1. Of these, 655 (62%) patients had tumors in the upper rectum, and 402 (38%) in the lower rectum. Five patients received preoperative radiotherapy; the reasons for radiotherapy were not described. Forty-nine patients (4.6%) had previously undergone tumor removal by transanal or endoscopic resection. Stage 0 or I disease was present in 578 (54.7%) patients. Anterior resection with double stapling technique was performed in 888 (84.0%) patients and hand-sutured coloanal anastomosis was performed in 107 patients (10.1%) patients, whereas abdominoperineal resection or

Table 1 Patient details

Number of patients	1,057
Sex (male/female)	665/392
Age (years)[a]	62.9 ± 11.7
BMI (kg/m^2)[a]	22.9 ± 3.2
Location of tumor	
Upper rectum	655
Lower rectum	402
Preoperative radiation	5 (0.5)
Previous tumor removal	49 (4.6)
Type of tumor	
Well/moderate	1023 (96.8)
Poor	11 (1.0)
Others	23 (2.2)
TNM stage	
0	83
I	495
II	197
III	230
IV	52
Procedures	
Anterior resection with double stapling technique	888 (84.0)
Anterior resection with sutured coloanal anastomosis	107 (10.1)
Abdominoperineal resection	50 (4.7)
Hartmann's procedure	10 (0.9)
Others	2 (0.2)
Diverting ileostomy	116

[a] Values are mean ± standard deviation; BMI, body mass index

Numbers in parentheses are percentages

Hartmann's procedure was performed in only 60 (5.6%) patients. A diverting ileostomy was fashioned in 20 (3.0%) patients in the upper rectum and 96 (23.9%) patients in the lower rectum. Conversions to open procedures occurred in 77 (7.3%) patients; the reasons for the conversions are shown in Table 2. Intraopearative complications occurred in 52 (4.9%) patients, including trouble in anastomosis in 17, uncontrollable bleeding in 15, injuries to other organs in 10, and others in 10. Operative and postoperative outcome are shown in Table 3. Operative time was significantly shorter and blood loss was significantly less for upper rectal cancer than for lower rectal cancer (250 versus 300 min, $p < 0.001$; 56 versus 150 ml, $p < 0.01$). Median length of postoperative hospital stay was 15 days (7–271 days). Patients with upper rectal cancer had shorter hospital stay than those with lower rectal cancer (14 versus 18 days, $p < 0.01$). Mean number of dissected lymph nodes was 15, which did not differ between the upper and lower rectal cancers.

Table 2 Reasons for conversions to open surgery

Trouble in anastomosis	15 (19.5)
Advanced disease	12 (15.6)
Narrow pelvic cavity	12 (15.6)
Adhesion	10 (13.0)
Obesity	7 (9.1)
Bleeding	5 (6.5)
No visualization of the location of tumor	5 (6.5)
Injury to other organs	3 (3.9)
Others	8 (10.4)
Total	77

Numbers in parentheses are percentages

Postoperative surgical and nonsurgical complications were seen in 278 (26.3%) patients (Table 4). Incidence of anastomotic leakage, which was the most common postoperative complication, was 9.1%. Of these, 36 patients were reoperated. There was no mortality within 30 days after surgery.

Curative surgery was performed in 1011 cases (95.6%). The reasons for noncurative surgery were liver metastasis in 28 cases, lung metastasis in 9, peritoneal dissemination in 6, and other metastases in 9 cases. The mean follow-up

Table 3 Operative and postoperative outcomes

Operative time (min)[a]	270 (122–780)
Blood loss (ml)[a]	90 (0–1800)
Time to oral intake (days)[a]	2 (1–70)
Time to first stool (days)[a]	4 (0–31)
Length of stay (days)[a]	15 (6–270)

[a] Values are median (range)

Table 4 Postoperative complications

Surgical complications, *n* (%)	235 (22.2)
Anastomotic leakage	84 (9.1)[a]
Wound infection	71 (6.7)
Bowel obstruction	38 (3.6)
Bleeding (including bleeding from anastomotic site)	15 (1.4)
Abscess	11 (1.0)
Others	16 (1.5)
Nonsurgical complications (%)	43 (4.1)
Urinary	16 (1.5)
Peripheral nerve	13 (1.2)
Pulmonary	6 (0.6)
Liver	2 (0.1)
Others	6 (0.6)
Mortality	0 (0)

[a] Patients undergoing Hartmann's procedure or abdominoperineal resection were excluded

Numbers in parentheses are percentages

Table 5 Recurrences and 3-year disease-free survival

Site of recurrence (%)	72
Lung	23 (31.9)
Liver	21 (29.2)
Local	11 (15.3)
Peritoneum	4 (5.7)
Others	13 (5.6)
Three-year disease-free survival (%)	
TNM stage	
0	100
I	94.6
II	82.4
III	79.7

Numbers in parentheses are percentages

period was 906 days (5–4,185 days). Recurrence was developed in 67 patients (6.6%) of the 1,011 curatively treated patients. The site of the first recurrence was the liver in 21 cases, the lung in 23, the local in 11, the peritoneum in 4, and other sites in 13 cases. The recurrence was detected during the first year in 22 patients and during the second year in 28 patients. There was no port-site metastasis. Of the 1,011 curatively treated patients, the 3-year disease-free survival rate was 100% in stage 0, 94.6% in stage I, 82.1% in stage II, and 79.7% in stage III (Table 5).

Discussion

The present study showed that laparoscopic surgery for rectal cancer is safe and feasible, with a low conversion rate, and provided favorable short-term and mid-term outcome. Conversion to open surgery occurred in 77 patients (7.3%), which was low compared with previously published data (10–30%) [1, 4, 5, 11, 12]. A low conversion rate was also reported by a few specialized centers [19, 26]. One of the reasons for the low conversion rate may be that the present study included a selected group of patients with rectal cancer, i.e., mainly early rectal cancer, which means that bulky, advanced tumors were not included. A bulky tumor in the narrow male pelvis is one of the reasons for conversion. Another reason might be that very few Japanese patients were overweight, the mean body mass index in the present study being less than 23 kg/m^2. The other reason might be that the definition of conversion was an incision more than 8 cm, which was liberal. Some procedures can be carried out with an incision of 8 cm in thin patients under direct vision, however, length of incision was the only parameter that could be collected in a multicenter, retrospective study. Conversion itself is not necessarily a negative event, but the appropriate incidence of the conversion is difficult to determine, however, the authors think that good selection of patients is reasonable and justified, considering that the patients with conversion had a higher incidence of postoperative complications than those without conversion in other studies [13].

The overall morbidity in the present study was 26%, which compares favorably with the published data of 53% in open procedures [3]. The most common postoperative complication was anastomotic leakage, with an incidence of 9.1%, which is consistent with published reports that report incidence in the range from 7% to 17% [5, 19, 20, 24]. Several risk factors have been reported be associated with postoperative complications, especially anastomotic leakage, including male sex, obesity, and the level of anastomosis [21, 23]. There are several reports on higher anastomotic leak rates after total mesorectal excision than in conventional surgery [3, 14]. Although some authors reported leak rates less than 5% after total mesorectal excision [26], others reported leak rates as high as 10–20% [3, 10]. The incidence of anastomotic leakage in laparoscopic rectal surgery seems to be higher than that in open surgery, however, there are some reports showing no differences in leak rates between the laparoscopic and open procedures [11, 20].

One technical factor could be one of the reasons for the higher leakage rates in laparoscopic rectal surgery. In the double stapling technique, the circular stapler used in laparoscopic procedures is basically the same as in open procedures, whereas the linear staplers are different. Some surgeons in the present study group used laparoscopic linear staplers through a suprapubic port to transect the rectum intracorporeally. Although articulated staplers are now available, at least two, or sometimes three or four, linear staplers are needed, thus resulting in an unduly long staple line. An unduly long staple line could be a reason for the higher leakage rate, although there are no data regarding the number of linear staplers used and the incidence of anastomotic leakage. Some surgeons in this group attempted to use a conventional linear stapler such as the TA stapler (Tyco, USA), Roticulator (Tyco, USA) or Access (Ethicon Endo-Surgery Inc., Cincinnati, USA), for open procedures through a small incision under direct view, which is sometimes difficult because it provides poor visualization of the deep narrow pelvis through a small incision. Recently, a new curved cutter stapler has become available, and its application to laparoscopic anterior resection might be a good alternative [15].

A diverting ileostomy was fashioned at the surgeon's discretion in the present study. The incidence of a diverting stoma for the lower rectum was 23.9% in the present study, which may be somewhat high. Some surgeons routinely fashion a diverting ileostomy for laparoscopic anterior

resection for rectal cancer [18]. The presence of a stoma does not prevent the development of anastomotic leakage, however, it can prevent a subsequent disaster.

One may criticize the relatively long postoperative hospital stay of 14 days in the present study. Because most Japanese insurance schemes cover the complete cost of hospitalization, there is still little incentive for early discharge. As a result, length of hospital stay is not yet a major concern for both patients and surgeons, which is a completely different situation from that in Western countries.

This study had several limitations in that it included only selected patients with rectal cancer because the indications for laparoscopic surgery expanded gradually as the authors gained experience, and the indications differed among the institutions. Patients with far advanced rectal cancer were not included and, when surgery was indicated, open procedures were adopted. Therefore, this study was not intended to be a strict comparison of open with laparoscopic procedures, and the mid-term or long-term outcome may be irrelevant. Neoadjuvant therapy has not been established and surgery is the first choice for rectal cancer in our country. Another study on preoperative chemoradiation for lower rectal cancer is now running. In the next study, preoperative chemoradiation may be a choice of treatment for lower rectal cancer. Only five patients receiving preoperative radiation or chemoradiation were included, and the feasibility of laparoscopy in these patients should also be evaluated in the future. Although the incidence of anastomotic leakage was 9.1% in the present study, which was comparable to other studies, the incidence of a diverting stoma was high. A prospective phase II study is being conducted by the authors' group to elucidate this matter, and a randomized controlled trial should be conducted to clarify the benefits of laparoscopic surgery for rectal cancer; however, the authors believe that the findings of the present study are of value in proposing the future studies.

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References

1. Anthuber M, Fuerst A, Elser F, Berger R, Jauch K-W (2003) Outcome of laparoscopic surgery for rectal cancer in 101 patients. Dis Colon Rectum 46:1047–1053
2. Barlehner E, Benhidjeb T, Anders S, Schicke B (2005) Laparoscopic resection for rectal cancer. Surg Endosc 19:757–766
3. Carlsen E, Schlichting E, Guldvog I, Johnson E, Heald RJ (1998) Effect of the introduction of total mesorectal excision for the treatment of rectal cancer. Br J Surg 85:526–529
4. Clinical Outcomes of Surgical Therapy Study Group (2004) A comparison of laparoscopically assisted and open colectomy for colon cancer. N Eng J Med 350:2050-2059.
5. Delgado S, Momblan D, Salvador L, Bravo R, Castells A, Ibarzabal A, Pique JM, Lacy AM (2004) Laparoscopic-assisted approach in rectal cancer patients: lessons learned from >200 patients. Surg Endosc 18:1457–1462
6. Dennis H, Jeanine T, Mehran A (2001) Laparoscopic vs. open resection for colorectal adenocarcinoma. Dis Colon Rectum 44:10–19
7. Enker WE, Thaler HT, Cranor ML, Polyak T (1995) Total mesorectal excision in the operative treatment of carcinoma of the rectum. J Am Coll Surg 181:335–346
8. Falk PM, Beart RW Jr, Wexner SD, Thorson AG, Jagelman DG, Lavery IC, Johansen OB, Fitzgibbons RJ Jr (1993) Laparoscopic colectomy: a critical appraisal. Dis Colon Rectum 36:28–34
9. Franklin ME Jr, Rosenthal D, Abrego-Medina D, Dorman JP, Glass JL, Norem R, Diaz A (1996) Prospective comparison of open vs. laparoscopic colon surgery for carcinoma: five-year results. Dis Colon Rectum 39:S35–S46
10. Goldberg S, Klas JV (1998) Total mesorectal excision in the treatment of rectal cancer: a view from the USA. Semin Surg Oncol 15:87–90
11. Guillou PJ, Quirke P, Thorpe H, Walker J, Jayne DG, Smith AMH, Heath RM, Brown JM for the MRC CLASICC trial group (2005) Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial); multicentre, randomised controlled trial. Lancet 365: 1718–1726.
12. Hainsworth PJ, Egan MJ, Cunliffe WJ (1997) Evaluation of a policy of total mesorectal excision for rectal and rectosigmoid cancers. Br J Surg 84:652–656
13. Heald RJ, Karanjia ND (1992) Results of radical surgery for rectal cancer. World J Surg 16:848–857
14. Ishii Y, Hasegawa H, Nishibori H, Endo T, Kitajima M (2006) The application of a new stapling device for open surgery

(Contour(TM) Curved Cutter Stapler) in the laparoscopic resection of rectal cancer. Surg Endosc. 20:1329–1331
15. Japanese Society for Cancer of the Colon and Rectum. General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus, 6th edn (in Japanese) (1998). Kanehara, Tokyo, Japan
16. Khallili TM, Fleshner PR, Hiatt JR, Sokol TP, Manookian C, Tsushima G, Phillips EH (1998) Colorectal cancer: comparison of laparoscopic with open approaches. Dis Colon Rectum 41:832–838
17. Lacy AM, Garcia-Valdecasas JC, Delgado S, Castells A, Taura P, Pique JM, Visa J (2002) Laparoscopy-assisted colectomy versus open colectomy for treatment of non-metastatic colon cancer: a randomised trial. Lancet 359:2224–2229
18. Leroy J, Jamali F, Forbes L, Smith M, Rubino F, Mutter D, Marescaux J (2004) Laparoscopic total mesorectal excision (TME) after rectal cancer surgery: long-term outcomes. Surg Endosc 18:281–289
19. Leung KL, KwokSPY Lam SCW, Lee JFY, Yiu RYC, Ng SSM, Lai PBS (2004) Laparoscopic resection of rectosigmoid carcinoma: prospective randomized trial. Lancet 363:1187–1192
20. Morino M, Parini U, Giraudo G, Salval M, Brachet CR, Garrone C (2003) Laparoscopic total mesorectal excision: a consecutive series of 100 patients. Ann Surg 237:335–342
21. Peeters KC, Tollenaar RA, Marijnen CA, Klein Kranenbarg E, Steup WH, Wiggers T, Rutten HJ, van de Velde CJ; Dutch Colorectal Cancer Group (2005) Risk factors for anastomotic failure after total mesorectal excision of rectal cancer. Br J Surg 92:211–216
22. Poulin EC, Mamazza J, Schlachta CM, Gregoire R, Roy N (1999) Laparoscopic resection does not adversely affect early survival curves in patients undergoing surgery for colorectal adenocarcinoma. Ann Surg 229:487–492
23. Rullier E, Laurent C, Garrelon JL, Michel P, Saric J, Parneix M (1998) Risk factors for anastomotic leakage after resection of rectal cancer. Br J Surg 85:355–358
24. Scheidbach H, Schneider C, Konradt J, Barelehner E, Kohler L, Wittekind Ch, Kockerling F (2002) Laparoscopic abdominoperineal resection and anterior resection with curative intent for carcinoma of the rectum. Surg Endosc 16:7–13
25. Wexner SD, Cohen SM (1995) Port site metastases after laparoscopic colorectal surgery for cure of malignancy. Br J Surg 82:295–298
26. Yamamoto S, Watanabe M, Hasegawa H, Kitajima M (2002) Prospective evaluation of laparoscopic surgery for rectosigmoidal and rectal carcinoma. Dis Colon Rectum 45:1648–1654
27. Young-Fadok TM, Radice E, Nelson H, Harmsen WS (2000) Benefits of laparoscopic-assisted colectomy for colon polyps: a case-matched series. Mayo Clin Proc 75:344–348
28. Zaheer S, Pemberton JH, Frouk R, Dozois RR, Wolff BG, Ilstrup D (1998) Surgical treatment of adenocarcinoma of the rectum. Ann Surg 227:800–811

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原著

大腸癌に対する腹腔鏡補助下大腸切除術
—開腹移行の術後経過に対する影響—

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Key words ◆ 腹腔鏡補助下大腸切除術，開腹移行，術後合併症

◆**要旨**：腹腔鏡補助下大腸手術開腹移行症例の術後経過に対する影響を検討した．**対象および方法**：2002～2005年までに施行した開腹移行症例（Con群：n＝11）と，腹腔鏡下手術完遂症例（Lap群：n＝264），開腹手術症例（Open群：n＝221）の術後合併症，術後在院日数について比較検討した．**結果**：Con群の術後合併症発生率は，Lap群と比較して有意に高かったが，Open群とは有意差を認めなかった．Con群は術後平均在院日数がLap群より2.9日延長し有意に長かったが，Open群との間に有意差は認めなかった．**結論**：開腹移行により術後回復は遅れたが，開腹術に比べ遜色なかった．

はじめに

近年，大腸癌での腹腔鏡補助下手術（laparoscopy-assisted colorectal surgery：以下，LAC）は急速に普及し，開腹手術と同等の手技を施行できるようになってきたが，開腹移行に至る症例は文献的に2～40％と報告[1]されている．開腹移行と術後合併症との関連を検討した海外文献は散見され[1-7]，腹腔鏡下手術に比べて合併症の増加[2,7]，術後在院日数の延長がみられるという報告がある[7]が，近年，開腹術との差はないという報告も出てきている[4,5]．医学中央雑誌，MEDLINEで「大腸」「開腹移行」「腹腔鏡」をキーワードに検索する限り，国内での同様の検討の報告はない．当院は，2002年9月の開院から2005年までに275例のLACを経験した．その間にわれわれが経験した開腹移行症例について検討し，開腹移行の術後経過に対する影響を検討した．

対象および方法

2002年9月の開院から2005年12月までに，大腸癌に対して当科で施行した，LAC 275例〔大腸全摘，人工肛門造設を伴う症例，ISR（intersphincteric resection）症例は除外〕と同時期の定型的開腹手術症例221例（他臓器直接浸潤，他臓器同時合併切除，人工肛門造設を伴う手術，ISR症例は除外），計496例を対象とした．当院でのLACの適応は，結腸癌とRS癌では

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表1 症例の背景

		Lap 群(n=264)	Con 群(n=11)	Open 群(n=221)	p 値(Lap 群 vs Con 群)
年齢（歳）		64.3±9.0(39～86)	64.3±14.5(33～85)	65.4±11.2(31～90)	0.726
性別（男性：女性）		158：106	7：4	86：135	1.000
BMI		22.9±3.3	24.7±3.9	22.5±3.4	0.148
開腹術既往（なし/あり）		230/34	7/4	166/55	0.050
占居部位	V	1	0	0	
	C	15	1	22	
	A	46	0	30	
	T	31	0	30	
	D	14	2	17	
	S	98	3	47	
	RS	36	2	35	
	Ra	16	2	25	
	Rb	7	1	15	
RS 以上/Ra 以下		241/23	8/3	181/40	0.074
病期	stage 0	13	0	3	
	stage Ⅰ	109	2	29	
	stage Ⅱ	86	5	71	
	stage Ⅲ	54	4	75	
	stage Ⅳ	2	0	43	
郭清	D0	0	0	3	
	D1	14	2	34	
	D2	90	3	35	
	D3	160	6	149	
手術時間(分)		214±59	249±78	171±52	0.131

病期に関しては，癌取扱い規約第7版に準じた．

StageⅡ以下を対象としており，直腸癌に対してはRaはT2まで，RbはT1までとしている．LAC症例を開腹移行群（Con群：n=11，開腹移行率4.0%）と，腹腔鏡下手術完遂群（Lap群：n=264）に分け，Con群とLap群の背景因子，手術時間に差があるか比較した．背景因子として，性別，年齢，BMI，虫垂切除術以外の開腹術既往，占居部位（RS以上とRa以下）を検討した．

また，術後合併症，術後在院日数に関してはCon群を，Lap群，定型的開腹手術群（Open群：n=221）とそれぞれ比較検討した．術後せん妄は術後合併症に含めなかった．開腹移行の定義は，通常のLAC手術創での手術継続が困難なため，予定より創を延長したものをすべてとした．HALSに移行して完遂した1例はLap群とした．

統計学的解析に関して，統計ソフトはDr.SPSSⅡを用いた．カテゴリーの比較にはFisher's exact testを，2群間の数値データの比較にはMann-Whitney's U testを用いた．変数は平均値±標準偏差で表記した．統計的有意差は$p<0.05$とした．

結　果

1．症例の背景（表1）

a）LAC症例の背景

Lap群およびCon群では，S状結腸癌が101例と最も多く，左側結腸が117例（42.5%）を占めた．病期に関してはfStageⅡ以下が215例（78.2%）と多くを占めた．当院ではcStageⅡ以下をLACの対象症例としているが，その結果，fStageⅢの症例も58例（21.1%）と多く含まれていた．郭清度に関してはD3郭清が166例（60.4%）と多くを占めた．

b）Con群とLap群の背景因子，手術時間の比較

両群間の背景因子として，検討項目においてはいずれも有意差を認めなかったものの，Con群

表2　開腹移行症例の詳細

症例	年齢	性別	部位	病期	開腹移行の原因	対処方法	術後合併症	術後在院日数
1	77	男	S	II	膀胱浸潤	開腹	創感染	10
2	64	男	D	II	後腹膜浸潤	開腹	なし	8
3	59	男	RS	II	膀胱浸潤	開腹	なし	7
4	64	女	S	I	癒着	開腹	創感染	16
5	76	女	S	IIIa	癒着	開腹	創感染	9
6	85	女	RS	II	高 CO_2 血症	開腹	なし	8
7	73	男	Rb	I	吻合困難	吻合時創延長	胆嚢炎	24
8	48	男	Ra	IIIa	点墨による炎症	開腹	なし	13
9	60	女	C	II	虫垂穿孔	小開腹	不明熱	8
10	68	男	Ra	IIIa	辺縁動脈損傷による腸管虚血	開腹	なし	20
11	33	男	D	IIIa	視野展開不良	開腹	なし	8

表3　術後合併症の比較

	Lap 群（n=264）	Con 群（n=11）	Open 群（n=221）
総数	36 例（13.6%）	5 例（45.5%） p=0.014（vs Lap 群）	69 例（31.2%） p=0.334（vs Con 群）
創感染	13 例（4.9%）	3 例（27.3%） p=0.020（vs Lap 群）	22 例（10.0%） p=0.102（vs Con 群）
縫合不全	8 例（3.0%）	0 例（0.0%） p=1.000（vs Lap 群）	16 例（7.2%） p=1.000（vs Con 群）
イレウス	6 例（2.3%）	0 例（0.0%） p=1.000（vs Lap 群）	20 例（9.0%） p=0.605（vs Con 群）

は開腹術既往を有する症例の割合が高い傾向があった（p=0.050）．また腫瘍局在部位に関して，Con 群は Ra 以下の病変の割合が高い傾向にあった（p=0.074）．手術時間に関しては両群間で有意差を認めなかった（p=0.131）．

2．開腹移行症例の詳細（表2）

Con 群を**表2**に呈示した．開腹移行は 11 例あり，開腹移行率は 4.0%だった．開腹移行の原因として，他臓器浸潤が 3 例，癒着が 2 例，高 CO_2 血症，吻合困難，点墨による炎症，切除腸管損傷，血管損傷による腸管虚血，肥満による視野展開不良が 1 例ずつであった．術後合併症としては，創感染を 3 例，胆嚢炎を 1 例，不明熱を 1 例経験した．再手術を要するような重篤な合併症は認めなかった．症例 7 は胆嚢炎保存的治療のため絶食を要したため，術後在院日数は 24 日だった．症例 10 は軽度の経口摂取障害があり，術後在院日数は 20 日を要した．

3．術後合併症の比較（表3）

術後合併症は，Lap 群で 264 例中 36 例（13.6%），Con 群で 11 例中 5 例（45.5%），Open 群で 221 例中 69 例（31.2%）に認めた．Lap 群と比較して，Con 群で術後合併症は有意に高かったが（p=0.014），Con 群と Open 群との間に有意差は認めなかった（p=0.334）．

創感染に関して比較すると，Lap 群で 264 例中 13 例（4.9%），Con 群で 11 例中 3 例（27.3%），Open 群で 221 例中 22 例（10.0%）に認めた．Lap 群と比較して，Con 群で創感染は有意に高かった（p=0.020）．Con 群は Open 群より創感染発生率は高かったが，有意差は認めなかった（p=0.102）．縫合不全，イレウスに関しては各群に差がなかった．

4．術後在院日数の比較（表4）

術後在院日数は，Lap 群で平均 9.0±6.2 日（中央値 8 日），Con 群で平均 11.9±5.7 日（中央値 9 日），Open 群で平均 12.7±8.5 日（中央値 10 日）であった．Lap 群と比較して Con 群で術後在院日数は有意に延長した（p=0.003）．Con 群は Open 群よりも短かったが，有意差は認めなかっ

表4　術後在院日数の比較

	Lap 群（n=264）	Con 群（n=11）	Open 群（n=221）
術後平均在院日数（日）	9.0±6.2	11.9±5.7	12.7±8.5
中央値（日）	8	9	10
p 値		p=0.003（vs Lap 群）	p=0.628（vs Con 群）

た（p=0.628）.

考　察

1991 年，Jacobs ら[8] が世界で初めて LAC を報告して以来，LAC は，開腹術に比べて術後回復が早く，術後在院期間の短縮が認められ[9,10]，手術侵襲が小さく[11]，術後合併症や創感染リスクの軽減，術後イレウスの減少[12] などの有効性が報告されている．良性疾患から悪性疾患に適応拡大され，結腸癌に対する LAC の遠隔成績に関して，海外では LAC の優位性を示した報告も認めるが[13]，本邦では JCOG による無作為比較試験が進行中である[14]．当科でも 2002 年の開院以来，積極的に大腸癌に対して LAC を施行してきた．

LAC の開腹移行率に関しては今日まで多くの報告がされているが，Gervaz ら[1] は，それらの 79%は開腹移行の定義なく検討されていることを指摘している．開腹移行の明確な定義は存在しないが，予定より早くまたは長く小開腹を置くこと[15] や，腹腔鏡操作を完全に中断して開腹下の手術に移行したもの[7]，手術創が 10 cm を超えたものまたは 10 cm 以下の創でも小開腹創から手術を施行したもの[5]，手術創が 6 cm を超えるものをすべて含む[16]，などのさまざまな定義が報告ごとになされているのが現状である．

今回のわれわれの検討では，通常の LAC 手術創での手術継続が困難になり予定より創を延長したものをすべて含めた．ドイツの Laparoscopic Colorectal Surgery Group の 1,658 例の検討[7] では開腹移行率は 5.2%であり，BMI が高値であること，直腸手術が開腹移行の危険因子と述べられている．また Gervaz ら[1] のメタアナリシスでは，開腹移行率は 2～40%と報告されており，開腹移行の危険因子として，左側結腸，直腸前方切除術，憩室・癌の手術であることが挙げられている．当科の開腹移行率は 4.0%であり，すべて大腸癌に対する手術であることを考慮すると比較的低値と考えられた．

開腹移行のリスク因子に関して今回の検討では有意差を持つものは認められなかったが，Ra 以下の病変，開腹術の既往という 2 つの因子に開腹移行が高い傾向を認めた．開腹術の既往は開腹移行の危険因子とはならないとの報告があるものの[15,17]，今回の検討では虫垂切除は癒着が軽度なものが多いという理由で開腹術の既往には含めなかったこともあり，一概に比較することはできない．

開腹移行症例の手術成績に関しての検討は少なく，海外の報告はいずれも良性疾患の手術症例が多数含まれていた．医学中央雑誌で検索した限り本邦での報告は認めなかった．開腹移行群に関して Falk ら[2] は，腹腔鏡群よりも合併症が多いことを報告している．ほかにも腹腔鏡群と比較して，イレウス，縫合不全，通過障害，合併症率，術後在院日数がいずれ増加したという報告[7] や，手術時間と術後在院日数の延長が認められた報告[1] もある．しかし，術後在院日数は延長するものの合併症率に差はないとする報告[4] も認める．

開腹移行症例の成績を開腹手術例と比較した検討としては，1995 年に Slim ら[6] が開腹移行群の手術時間，在院日数の延長と，合併症率，縫合不全の増加を報告している．Belizon ら[16] も同様に術後合併症の増加，在院日数の延長を報告しているが，この報告は大腸癌に対する手術を含んでいない．近年の報告のなかで Casillas ら[5] は，手術時間，術後在院日数，入院コスト，再入院率において差はないと報告しており，Gonzalez ら[4] は，術後在院日数は開腹群より短く，合併症率に差はないと述べている．LAC の経験が増してきたことにより開腹移行の適切な判断がなされるように

なり，このような良好な成績につながっている可能性が示唆される．

今回のわれわれの検討では手術時間はLap群とCon群で有意差を認めていない．術中早い段階での適切な開腹移行の決断が術後経過を良好にするという指摘があり[5,7,16]，これは開腹移行の適切な判断の指標になるかもしれない．

今回の検討では，Con群の合併症，特に創感染率はLap群よりも有意に増加したが，Open群との有意差は認めなかった．Con群の術後在院日数はOpen群と同等で，重篤な合併症も認めなかった．よって，開腹移行は，通常開腹術以上の不利益は認めなかった．

おわりに

開腹移行の明確な定義はなく，開腹移行の症例数が少ないうえでの検討だが，適切な判断のもとで行われる開腹移行は通常開腹術以上の不利益をもたらすものではなかった．

◆文献

1) Gervaz P, Pikarsky A, Utech M, et al : Converted laparoscopic colorectal surgery. Surg Endosc **15** : 827-832, 2001
2) Falk PM, Beart RW Jr, Wexner SD, et al : Laparoscopic colectomy : a critical appraisal. Dis Colon Rectum **36** : 28-34, 1993
3) Le Moine MC, Fabre JM, Vacher C, et al : Factors and consequences of conversion in laparoscopic sigmoidectomy for diverticular disease. Br J Surg **90** : 232-236, 2003
4) Gonzalez R, Smith CD, Mason E, et al : Consequences of conversion in laparoscopic colorectal surgery. Dis Colon Rectum **49** : 197-204, 2006
5) Casillas S, Delaney CP, Senagore AJ, et al : Does conversion of a laparoscopic colectomy adversely affect patient outcome? Dis Colon Rectum **47** : 1680-1685, 2004
6) Slim K, Pezet D, Riff Y, et al : High morbidity rate after converted laparoscopic colorectal surgery. Br J Surg **82** : 1406-1408, 1995
7) Marusch F, Gastinger I, Schneider C, et al : Importance of conversion for results obtained with laparoscopic colorectal surgery. Dis Colon Rectum **44** : 207-214, 2001
8) Jacobs M, Verdeja JC, Goldstein HS : Minimally invasive colon resection (laparoscopic colectomy). Surg Laparosc Endosc **1** : 144-150, 1991
9) Gibson M, Byrd C, Pierce C, et al : Laparoscopic colon resections : a five-year retrospective review. Am Surg **66** : 245-248, 2000
10) Tuech JJ, Pessaux P, Rouge C, et al : Laparoscopic vs open colectomy for sigmoid diverticulitis : a prospective comparative study in the elderly. Surg Endosc **14** : 1031-1033, 2000
11) Chen HH, Wexner SD, Weiss EG, et al : Laparoscopic colectomy for benign colorectal disease is associated with a significant reduction in disability as compared with laparotomy. Surg Endosc **12** : 1397-1400, 1998
12) Chen HH, Wexner SD, Iroatulam AJ, et al : Laparoscopic colectomy compares favorably with colectomy by laparotomy for reduction of postoperative ileus. Dis Colon Rectum **43** : 61-65, 2000
13) Lacy AM, Garcia-Valdecasas JC, Delgado S, et al : Laparoscopy - assisted colectomy versus open colectomy for treatment of non-metastatic colon cancer : a randomised trial. Lancet **29** : 2224-2229, 2002
14) Kitano S, Inomata M, Sato A, et al : Randomized controlled trial to evaluate laparoscopic surgery for colorectal cancer : Japan Clinical Oncology Group Study JCOG 0404. Jpn J Clin Oncol **35** : 475-477, 2005
15) Schwandner O, Schiedeck TH, Bruch H : The role of conversion in laparoscopic colorectal surgery : Do predictive factors exist? Surg Endosc **13** : 151-156, 1999
16) Belizon A, Sardinha CT, Sher ME : Converted laparoscopic colectomy : what are the consequences? Surg Endosc **20** : 947-951, 2006
17) Huscher C, Silecchia G, Croce E, at al : Laparoscopic colorectal resection. A multicenter Italian study. Surg Endosc **10** : 875-879, 1996

Consequences of conversion from laparoscopy-assisted surgery to laparotomy for patients with colorectal cancer

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Purpose : The purpose of this study is to evaluate and compare the outcomes of patients whose laparoscopy-assisted surgery was converted to laparotomy, with those undergoing laparoscopic and open colorectal resections. **Methodology** : We reviewed 496 patients with consecutive colorectal resections performed between 2002 and 2005. Patients were divided into 3 groups according to the surgical procedures : conversions from laparoscopy-assisted surgery to laparotomy (Con : n=11), laparoscopic colorectal resections (Lap : n=264), and open colorectal resections (Open : n=221). Operative outcomes were compared between Con and the other 2 groups. **Results** : Con group was associated with significantly more morbidity than Lap group but no significant difference was observed with Open group. Con group was associated with longer hospital stay (2.9 days) compared to Lap group but there were also no significant difference between Open group. **Conclusions** : Conversion from laparoscopy-assisted surgery to open colorectal resection does not result in worse outcomes than open colorectal resections.

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症例報告

FDG-PET/CTにて高度進行大腸癌と術前診断した，悪性リンパ腫を合併した上行結腸癌の1例

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A Case of Ascending Colon Cancer which was Overdiagnosed by Preoperative FDG-PET/CT because of the Coexisting of Malignant Lymphoma.

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症例は61歳，女性。血尿の精査のため近医で施行した腹部CT検査にて回盲部周辺のリンパ節腫大を指摘された。下部内視鏡検査にて上行結腸癌を指摘され紹介となった。FDG-PET/CTにて上行結腸癌の領域リンパ節を中心にリンパ節腫大を認めたほか，大動脈周囲リンパ節の腫大と腹腔内結節が散見され，それぞれFDGの集積を認めた。領域外リンパ節転移・腹膜転移を伴う上行結腸癌(cStage IV)と診断した。腹腔鏡にて腹腔内病巣を観察したところ，腹膜転移はみられず根治手術が可能と判断し，そのまま腹腔鏡補助下に回盲部切除＋D3郭清を施行した。病理組織学的所見は悪性リンパ腫を合併した上行結腸癌であった。近年，大腸癌の術前病期診断にPET/CTの有用性が注目されているが，大腸癌・悪性リンパ腫ともにFDGを集積するため，とくにリンパ節転移の診断には注意を要すると思われる。また腹腔鏡での観察は，その鑑別に有用と考えられる。

索引用語：大腸癌(colorectal cancer)，腹腔鏡手術(laparoscopic surgery)，悪性リンパ腫(malignant lymphoma)

緒　言

近年，大腸癌の術前の病期診断や術後の再発診断に，FDG-PET/CT (^{18}F-fluorodeoxy-glucose positron emission tomography combine with CT scanning；以下PET/CTと略す）の有用性が注目されている[1)-3)]。今回われわれは，上行結腸癌の術前PET/CTにて領域外リンパ節への転移を指摘されたが，実際は悪性リンパ腫の合併であった稀な1例を経験した。癌の治療方針を決定する上で，最も重要なことは，正確な診断と進行度の把握であるが，本症例のような場合，PET/CTの所見から時には手術適応の判断を誤る可能性もあり，注意を要すると思われたため報告する。

症　例

患者：61歳，女性。
主訴：血尿。
既往歴：特記すべきことなし。
家族歴：兄，肝臓癌。

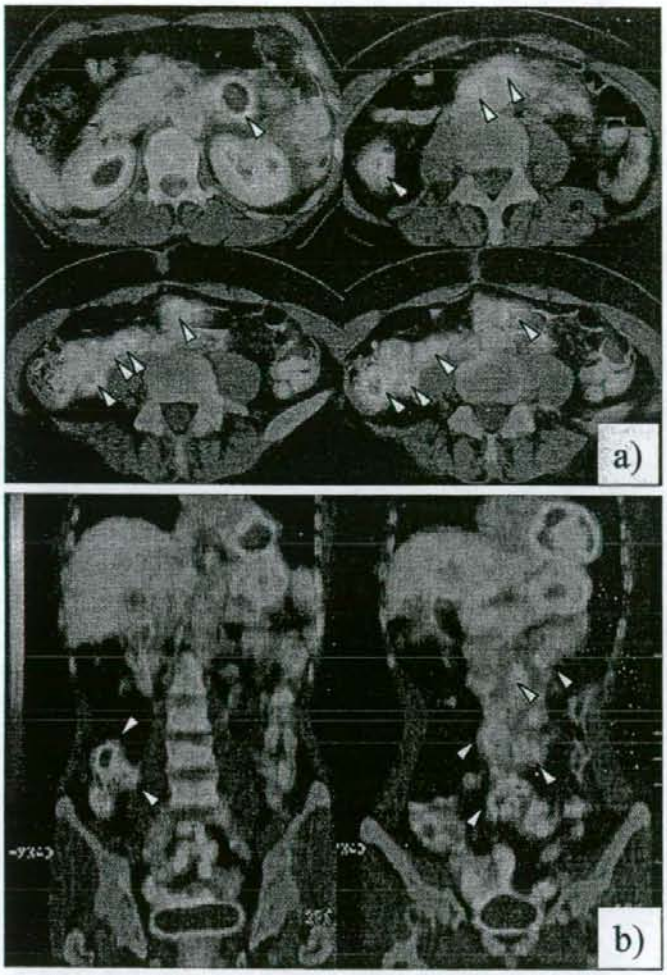

Fig. 4　a) axial view, b) coronal view. PET/CT showed the hot spot (arrow) at the primary colon cancer, swollen regional and para-aaortic lymph nodes and intra-abdominal nodules which suspected lymph nodes and peritoneal metastases.

症例を経験した。画像診断の進歩により重複癌の報告が多くなってきているが，本症例のように大腸癌と悪性リンパ腫が同時性に併存する症例は少ない[8)9)]。本症例は，術前，領域外リンパ節転移・腹膜転移を伴う上行結腸癌と診断され，悪性リンパ腫は疑われなかった。回盲部付近のリンパ節が最も腫大していたことから，この部位が悪性リンパ腫の原発と推察されるが，他のリンパ節を含め大腸癌の領域リンパ節と偶然一致してリンパ節へのFDGの集積を認めた。さらに大動脈周囲リンパ節や腹腔内結節と思われる集積もみられ，本来は悪性リンパ腫によるFDGの集積であったものが大腸癌の転移とoverdiagnosisされた。遠隔転移が確定診断されれば化学療法の適応となるが，化学療法のみで根治する可能性はきわめて低いこと，本症例のような大腸癌の原発巣(cSS，長径 3 cm 大，1/3周性)からでも高度のリンパ節転移（N3 M1(No216)）や腹膜転移（P 3）をきたす可能性はあるにせよ少ないことから，さらに正確な診断をして治療方針を決める必要があると考えた。そこで，患者への十分な説明と同意を得た上でまず腹腔鏡を施行し，迅速標本を提出して大腸癌の回

腸根リンパ節転移や腹膜転移を否定することができた。結果として大腸癌に対しては根治手術が可能となり，腹腔鏡による診断は非常に有用であった。悪性リンパ腫の腫大リンパ節は，大腸癌の転移リンパ節に比べて鉗子による把持で比較的柔らかい印象があり，周囲組織への浸潤傾向もなかったが，両者の正確な鑑別は困難で，迅速病理診断は必要であると思われた。

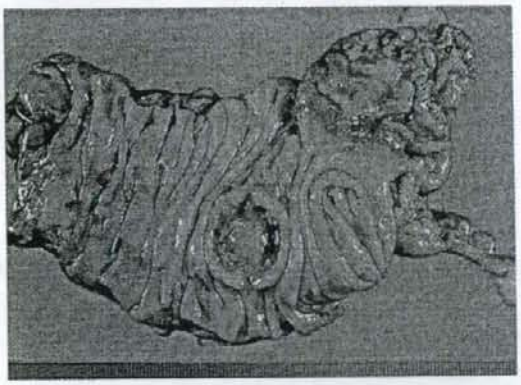

Fig. 5 Resected specimen showed the tumor of 3 cm in diameter at the ascending colon and the developed lymphoid follicles at the terminal ileum.

本症例においてretrospectiveにCTとPET/CTを検証すると，腹水がないこと，腹腔内結節が骨盤内ではなく上腹部を中心に認めること（これは術中所見での小腸間膜内のリンパ節腫大の所見と合致する）から，少なくとも腹膜転移とのover-diagnosisは防ぎ得たのではないかと反省している。

PET/CTは全身を評価できるため，副産物として予期せぬ病変が検出されることがあり，重複癌のスクリーニングとしても臨床的に有用性が高いといわれる[5]。しかし，一方では本症例のように手術適応の判断を誤る可能性もあり，とくにリンパ節転移の診断には注意を要する。リンパ節に広範囲にFDGの集積を認めた場合など，悪性リンパ腫の重複も念頭におく必要があると思われる。また，腹腔鏡はその鑑別に非常に有用と考えられる。

おわりに

PET/CTにて高度進行大腸癌とoverdiagnosisされた悪性リンパ腫を合併した上行結腸癌の1手術例を経験した。PET/CTは確かに診断治療に有用なツールであるが，本症例のようにover-

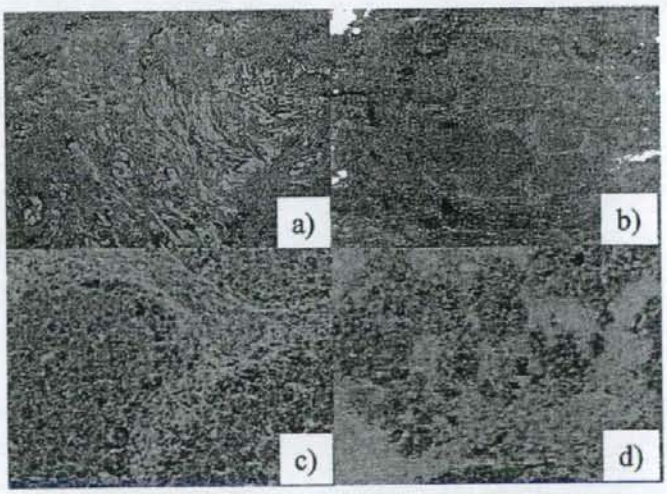

Fig. 6 The findings of Pathological and Immuno-histochemistry Microscopy showed the mucinous adenocarcinoma at the colon cancer (a), small round lymphocytes infiltration at all the dissected lymphnodes (b). Immunohistochemistry showed that the CD10 (c) and CD79a (d) stains were positive. (H.E. a×200, b×100, CD10. c×200, CD79a. d×400)

diagnosisの可能性もあり，注意を要すると思われたため報告した。

参考文献

1) Llamas-Elvira JM, Rodriguez-Fernandez A, Gutierrez-Sainz J, et al : Fluorine-18 fluorodeoxyglucose PET in the preoperative staging of colorectal cancer. Eur J Nucl Med Mol Imaging 34 : 859-867, 2007
2) 加藤貴司，中川学，中川宗一他：全身18F-FDG-PET検査による大腸腫瘍の検出能の検討．日大腸検会誌19：88-91，2002
3) 村上康二，黒木嘉典，那須克宏他：大腸癌リンパ節転移におけるFDG-PETの有用性の検討．日本医放会誌62：S91，2002
4) Subhas N, Patel PV, Pannu HK, et al : Imaging of pelvic malignancies with in-line FDG PET-CT : case examples and common pitfalls of FDG PET. Radiographics 25 : 1031-1043, 2005
5) 金子恒一郎，佐々木雅之，古賀博文他：外科領域におけるPETの意義と臨床応用　悪性リンパ腫．外科68：684-689，2006
6) Reinhardt MJ, Herkel C, Altehoefer C, et al : Computed tomography and 18F-FDG positron emission tomography for therapy control of Hodgkin's and non-Hodgkin's lymphoma patients : when do we really need FDG-PET? Ann Oncol 16 : 1524-1529, 2005
7) Tatsumi M, Cohade C, Nakamoto Y, et al : Direct comparison of FDG PET and CT findings in patients with lymphoma : initial experience. Radiology 237 : 1038-1045, 2005
8) 今津浩喜，船曳孝彦，落合正宏他：大腸癌切除時の郭清リンパ節に節性悪性リンパ腫を認めた1例．日臨外会誌59：1592-1595，1998
9) 杉原重哲，手島憲一，外山栄一郎他：結腸癌手術時のリンパ節に悪性リンパ腫を認めた2例．手術59：1879-1882，2005

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特集 大腸癌診療—最近の話題

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へるす出版

6. 局所進行直腸癌に対する放射線療法のコンセンサス

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小野里　航／内藤　正規／井原　厚／渡邊　昌彦
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はじめに

結腸癌は手術後の補助化学療法が標準治療となっているが，進行直腸癌の標準的治療は確立されていない。進行直腸癌の治療では，全生存率の向上のみならず，独特の再発形式である局所再発のコントロールが重要な課題である（表1）。全直腸間膜切除術（TME；total mesorectal excision）は，局所再発率の低下をもたらし，標準手術として認められている。一方，本邦で積極的に施行されている側方リンパ節郭清の意義に関しては，TMEを対照とした多施設共同無作為比較試験（RCT；randomized control trial）が行われており，この結果が待たれる。

補助療法として，術後化学放射線療法が無再発生存率を向上させたGITSG 7175[1]の結果から，米国のNIHはp-stage ⅡおよびⅢの直腸癌の標準治療として「切除＋術後化学放射線療法」を1990年から推奨している[2]。しかし，本邦では，欧米に比べて，手術単独での局所再発率が低いために，補助放射線療法の大規模な臨床試験はほとんど行われてこなかった。そのため，本邦での直腸癌に対する補助化学放射線療法の適応基準は明確ではない。

本稿では，局所進行直腸癌に対する補助化学放射線療法について述べる。

放射線療法vs.化学放射線療法

術前放射線療法単独治療における12の第Ⅲ相試験が報告され，このうち5件で手術単独療法に比べて有意に局所制御率が良好であった[3]。このうち，Swedish Rectal Cancer Trialでは，有意に生存率の向上を認めている（表2）[4]。

治癒切除可能直腸癌に対する術前補助放射線療法に関しての報告の多くが化学療法を併用しているが，術前放射線療法に化学療法を併用する意義を検討した大規模な臨床試験の報告はなかった。これらを受けてEORTCで，4群の比較試験が行われた（図1）。化学療法は5-FU/LV，放射線療法は1.8Gy×25日（総照射量45Gy）で行われた。その結果，化学療法の併用は，生存率の向上に寄与しなかった。しかし局所再発率は，A群17.1%，B群8.7%，C群9.6%，D群7.6%であり，5年局所再発の制御は実施時期に関わらず化学療法併用群が，放射線療法単独群に比べ有意に優れていた（3群に対して$p=0.002$）。この結果は，5-FUベースの化学療法を術前放射線療法に併用すること

表1　本邦における初発再発部位

再発部位	結腸 2746症例	直腸 1323症例	p値
肝	6.8%	7.3%	
肺	3.2%	6.7%	$p<0.0001$
局所	1.9%	7.6%	$p<0.0001$
吻合部	0.3%	0.6%	
その他	3.7%	4.4%	
全体	16.7%		

〔大腸癌研究会・プロジェクト研究　1991～1996年症例（大腸癌治療ガイドライン医師用2005年版より）〕

表2 Swedish Rectal Cancer Trial

手術単独 vs. 手術 + 術前補助放射線療法
(5Gy × 5days)
1987. 3 ~ 1990. 2 1168 症例

	術前照射群	手術単独群	p 値
生存	58%	48%	0.004
癌死亡	74%	65%	0.002
局所再発	11%	27%	< 0.001

(Påhlman L, et al, 1997 N Engl J Med)

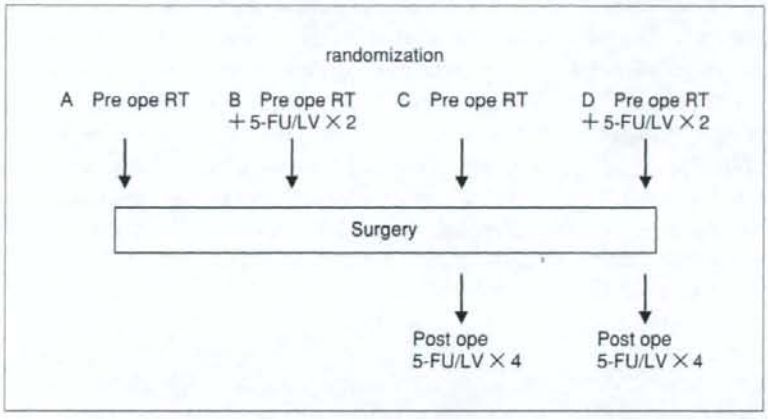

図1 EORTC 22921

の意義を明確にした[5]。

治療成績

Swedish Rectal Cancer Trialでは，術前化学放射線療法が生存率の向上に寄与することが報告されたが[4]，その他の大規模臨床試験での追報告はみられない。一方，Guillemらは術前化学放射線療法でCRまたはCRに近い効果の得られた症例の予後がよいことを報告した[6]。

Mohiuddinらの無作為化第Ⅱ相試験では，5-FUの持続静脈注射(225 mg/m²/day×持続5日/week)と総照射量55.2～60.2Gyの骨盤内照射群と，5-FUの持続静脈注射(225mg/m²/day×持続5日/week)にCPT-11(50mg/m²/回/week×4)および骨盤内照射 50.4～54Gyの2群比較を行った。結果として，両群ともに治療完遂率90%で，pCR率28%(T3：32%，T4：18%)が得られ，両群間に差は認めなかった[7]。

Calvoらが，術前化学放射線療法にinduction therapyとしてFOLFOX療法を加えた新しいレジメンを考案し報告した。経口抗癌剤を用いた術前化学放射線療法にFOLFOX4を加えた群は，化学放射線療法単独群と比較して，pT0へのダウンステージングが8%から29%(p=0.006)，pT0～1へのダウンステージング率が24%から44%(p=0.029)に有意に上昇したが，術後副作用の発現率は同等であった。放射線療法にFOLFOX療法を併用するのではなく，induction therapyとしてFOLFOX4を用いる方法は，安全かつ有効であることが示されている[8]。

一方，オキサリプラチンを用いた術前化学放射線療法として，CALGB89901が報告された。5-FU持続静脈注射(200mg/m²/day×7日)×6サイクルに，1回/weekのオキサリプラチン60mg/m²(第Ⅰ相試験にて決定)を投与した。治療完遂率は56%であったが，25%のpCR率が得られ，治療効果の高い有用な治療として，現在大規模臨床試験が行われている[9]。

おわりに

1990年のNIHの提言以降，直腸局所進行大腸癌の欧米での標準治療は，化学放射線療法と手術療法の併用である。本邦では，手術単独の治療成績がよいことから，化学放射線療法の検討が行われていないのが現状である。手術治療のRCTであるJCOG 0212，TME vs. TME＋側方郭清の治療成績の結果が待たれるが，今後本邦でも，補助化学放射線療法に関する大規模なRCTが行われることが望まれる。

文献

1) Gastrointestinal Tumor Study Group：Prolongation of the disease-free interval in surgically treated rectal carcinoma. N Engl J Med 312：1465～72, 1985.
2) NIH consensus conference：Adjuvant therapy for patients with colon and rectal cancer. JAMA 264：1444～50, 1990.
3) Skibber JM, et al：Cancer of the rectum. *In* Devita VT, eds. Cancer：Principles and Practice of Oncology. 6th ed, Lippincott, Williams and Wilkins, Philadelphia, 2001, p1271～318.
4) Improved survival with preoperative radiotherapy in resectable rectal cancer：Swedish Rectal Cancer Trial. N Engl J Med 336：980～7, 1997.
5) Bosset JF, et al：EORTC Radiotherapy Group Trial 22921：Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med 355：1114～23, 2006.
6) Guillem JG, et al：Long-term oncologic outcome following preoperative combined modality therapy and total mesorectal excision of locally advanced rectal cancer. Ann Surg 241：829～36；discussion 836～8, 2005.
7) Mohiuddin M, et al：Radiation Therapy Oncology Group Trial 0012：Randomized phase II study of neoadjuvant combined-modality chemoradiation for distal rectal cancer：Radiation Therapy Oncology Group Trial 0012. J Clin Oncol 24：650～5, 2006.
8) Calvo FA, et al：Improved incidence of pT0 downstaged surgical specimens in locally advanced rectal cancer (LARC) treated with induction oxaliplatin plus 5-fluorouracil and preoperative chemoradiation. Ann Oncol 17：1103～10, 2006.
9) Cancer and Leukemia Group B 89901, et al：Phase I/II study of preoperative oxaliplatin, fluorouracil, and external-beam radiation therapy in patients with locally advanced rectal cancer：Cancer and Leukemia Group B 89901. J Clin Oncol 24：2557～62, 2006.

Amphiregulin Is a Promising Prognostic Marker for Liver Metastases of Colorectal Cancer

Michiyo Yamada,[1] Yasushi Ichikawa,[1] Shigeru Yamagishi,[1] Nobuyoshi Momiyama,[1] Mitsuyoshi Ota,[2] Syoichi Fujii,[2] Kuniya Tanaka,[1] Shinji Togo,[1] Shigeo Ohki,[2] and Hiroshi Shimada[1]

Abstract **Purpose:** Aberrant activation of epidermal growth factor receptors (EGFR/HER1) by ligand stimulation or heterodimerization with human epidermal growth factor 2 (HER2) is considered to play an important role in the development of colorectal carcinoma. Amphiregulin (AR) is a ligand of EGFR that might be related to the development and progression of gastrointestinal tumors. The aim of this study was to determine the AR, EGFR, and HER2 protein expression levels and to evaluate their prognostic relevance to the clinical course of colorectal cancer.

Experimental Design: The AR, EGFR, and HER2 protein levels in primary tumors of colorectal cancer ($n = 106$) were examined using immunohistochemistry. Metastatic sites in liver specimens ($n = 16$) were also analyzed in the same manner.

Results: Thirteen (81.6%) metastatic lesions of the liver stained positive for AR. Among the primary lesions of colorectal cancer, 58 (54.7%) stained positive for AR, 13 (12.3%) stained positive for EGFR, and 5 (4.7%) stained positive for HER2. When the relationships between each protein expression level and the clinicopathologic factors were examined, only the AR expression level was significantly related to liver metastasis ($P = 0.0296$). A multivariate analysis of liver metastasis proved that AR expression was an independent prognostic factor of liver metastasis from colorectal cancer ($P = 0.0217$).

Conclusions: AR expression in primary lesions of colorectal cancer is an important predictive marker of liver metastasis.

Epidermal growth factor (EGF) receptors (EGFR) and their various ligands seem to be involved in the progression of gastrointestinal tumors (1). The EGF signal pathway is reportedly activated by several kinds of stimulation. First, ligands like amphiregulin (AR), transforming growth factor-α (TGF-α), and EGF may bind to EGFR. EGFR, a 170-kDa transmembrane glycoprotein (2), is composed of an extracellular ligand-binding domain, a transmembrane region, and an intracellular protein tyrosine kinase domain (3–5). The above-mentioned ligands bind to the extracellular ligand-binding domain of EGFR and stimulate the pathway. Second, the heterodimerization of EGFR and HER2 can reportedly stimulate signaling in the absence of ligands (2). These steps are followed by the stimulation of intrinsic tyrosine kinase activity and tyrosine autophosphorylation (3, 6–8). Receptor activity is modulated by intracellular kinases that mediate negative feedback control via receptor phosphorylation at specific regulatory domains, and receptor inactivation is mediated by receptor internalization and ligand-receptor dissociation. AR has been implicated in the growth and regeneration of intestinal mucosa and might be related to the development and progression of gastrointestinal tumors (9–12). Our microarray analysis in colorectal tumors and liver metastases revealed that AR was down-regulated in adenomatous tumors but was up-regulated in metastatic tumors of the liver (data not shown). These findings suggested that AR might contribute to liver metastasis from colorectal cancer. The aim of this study was to clarify the relationship between AR expression and liver metastasis and to uncover any correlations between the protein levels of AR, EGFR, and HER2 and the proliferation of colorectal cancer.

Materials and Methods

Human tissues. The study population comprised 106 consecutive patients who underwent the resection of colorectal cancer at the Department of Gastroenterologic Surgery, Yokohama City University Hospital. The patient characteristics are described in Table 1. There is another figure, related to patient profile, which shows whether each case has liver metastasis. There were 106 cases. Eighteen cases had synchronous liver metastasis at the surgical treatment of a primary tumor. In 88 cases, there were no liver metastases, but in the remaining 18, liver metastases occurred later. This analysis of the investigation has three parts: The first is concerned with the correlation between the pathologic factors and protein expression and liver metastases; the second about overall survival, or disease-free survival; and the third, about metachronous liver metastases (Fig. 1).

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