成時，腹直筋後鞘に達すると，癒着が強くなって，はがれなくなる．最近では，無理にはがさずに前鞘と後鞘の縦切開線をずらし，後鞘は外側縁としている．皮膚縁から5 cm以上結腸断端の血行を確認して，持ち上げておく．骨盤死腔感染予防に最も優れている方法として，右下腹部から骨盤腔への持続吸引ドレーン挿入（ポータブル低圧持続吸引器；50 mmHgで吸引）[10]を行う．骨盤底腹膜は骨盤底への癒着防止のため，4-0 PDSにて連続縫合する．創への癒着予防として，セプラフィルムを創直下に貼付する．腹壁は，下方のみ腹膜のみで縫合する．筋層は0-PDS　ループ針による連続縫合を行う．皮膚は4-0 PDSによる連続埋没縫合とする．皮膚創をダーマボンドを塗布する．

7 ストーマの形成

皮膚縁から3 cmの長さで切離する．間膜脂肪が厚い場合は血行を障害しないように腹膜を切除して脂肪をそぐ．1.5 cmの高さになるように断端を外翻する．腸管断端，漿膜筋層（あるいは間膜漿膜），皮下を4-0 PDSにて埋没縫合する．合計8〜10針．粘膜皮膚接合部は絶対陥凹しないよう，むしろ皮膚より少し高い位置になるようにする．また，血行が悪いと思ったら，再開腹しても，そのときに再造設する．血行障害により，強い狭窄をきたしたストーマの管理は，その後の人生で難渋をきわめるためである．

8 術後管理

術直後は循環動態，後出血の有無に気をつける．特に側方郭清を行った場合，剝離面が広く，止血された静脈が露出しているので，持続吸引は第1病日から行う．食事は3日目から流動食，3分粥，全粥と，1日ごとに段階をあげる．会陰部抜糸は10日目としている．

おわりに

局所解剖を理解し，剝離層を見きわめる手技は，出血を少なくし，機能温存の可能性を高め，癌遺残の少ない手術をするための基本である．臨床局所解剖学の知見が増えてきており，さらに本術式の完成度が高まる期待が大きい．一方，ケアのしやすいストーマ造設も，本術式の大きな要素であることを銘記すべきである．

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Introduction of laparoscopic low anterior resection for rectal cancer early during residency: a single institutional study on short-term outcomes

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Abstract
Background Laparoscopic surgery for rectal cancer is unpopular because it is technically challenging. Suitable training systems have not been widely studied or established despite the steep learning curve for this procedure. We developed a systematic training program that enables resident surgeons to perform laparoscopic low anterior resection (LLAR) for rectal cancer and evaluated the safety and feasibility of this training program.
Methods We analyzed prospectively gathered data on all LLARs for rectal cancer performed at a single center over a 7-year period. Patients were assessed for demographic characteristics, tumor characteristics, operative procedure, operative time, blood loss, conversion to open surgery, complications, time to bowel recovery, distal margin, and number of lymph nodes harvested. We compared the early surgical, oncological, and functional outcomes of LLARs performed by expert surgeons with those of LLARs performed by resident surgeons for both intraperitoneal and extraperitoneal rectal cancer. All analyses were performed on an intention-to-treat basis.
Results A total of 137 patients met the inclusion criteria for this study. Of the 75 LLARs for intraperitoneal rectal cancer, 40 were performed by expert surgeons (I-E group) and 35 by resident surgeons (I-R group). Of the 62 LLARs for extraperitoneal rectal caner, 51 were performed by expert surgeons (E-E group) and 11 by resident surgeons (E-R group). The operative time was longer in the E-R group than in the E-E group. The time to resumption of diet was longer in the I-E group than in the I-R group. The other early outcomes, including blood loss, anastomotic leakage, conversion to open surgery, and number of lymph nodes harvested, were similar in the I-E and I-R groups and in the E-E and E-R groups.
Conclusion Our systematic training program on LLAR for rectal cancer enables resident surgeons to perform this procedure safely early during residency, with acceptable short-term outcomes.

Keywords Laparoscopic training · Low anterior resection · Rectal cancer · Education · Residency · Minimally invasive surgery

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Some authors have reported that laparoscopic surgery for rectal cancer is safe and efficacious because it is associated with less pain and blood loss, early bowel recovery, and short postoperative hospital stay [1–6]. A few randomized studies have shown that laparoscopic total mesorectal excision (TME) and lymphadenectomy can be adequate treatments for rectal cancer and that the subsequent recurrence and survival rates are similar to those after open surgery [4, 6–8]. However, laparoscopic surgery, which is the standard treatment for colon cancer, is not commonly performed for the treatment of rectal cancer. Laparoscopic surgery for rectal cancer is technically challenging and is

associated with some disadvantages such as long operative time [1, 2, 4] and increased rate of positive surgical margins [9]. Furthermore, suitable training systems for advanced laparoscopic procedures have not been widely studied.

We developed a systematic training program that offers sufficient experience in laparoscopic colorectal resections (LCRs) to resident surgeons without prior experience in open colorectal surgery and enables them to acquire the skills required to perform laparoscopic low anterior resection (LLAR) for rectal cancer. In this study we evaluated the safety and feasibility of allowing resident surgeons to perform LLAR for rectal cancer by comparing the early surgical, functional, and oncological outcomes of LLARs performed by expert surgeons with those of LLARs performed by resident surgeons for both intraperitoneal and extraperitoneal rectal cancer.

Patients and methods

Patients

We analyzed prospectively gathered data on all LLARs for rectal cancer performed at Kyoto Medical Center, Kyoto, Japan, between February 2001 and March 2008. Kyoto Medical Center actively supports an independent surgical residency program. The LLARs for intraperitoneal and extraperitoneal rectal cancer were performed by either expert surgeons (I-E group and E-E group, respectively) or resident surgeons (I-R group and E-R group, respectively).

Indication for laparoscopic surgery was rectal cancer without involvement of the lateral lymph nodes or invasion of the adjacent organs as determined during preoperative examination using computed tomography (CT) and pelvic magnetic resonance imaging (MRI). Evidence of metastatic disease that could not be curatively resected by open surgery was also an indication for laparoscopic surgery. Low anterior resection (LAR) is used for the treatment of early cancer located just above the dentate line and for treatment of advanced cancer located more than 1 cm above the dentate line; these criteria enable the acquisition of an adequate distal margin after transection of the rectum.

Patients were assessed for the following: demographic characteristics, tumor characteristics, operative time, blood loss, conversion to open LAR, complications including anastomotic leakage, and time to bowel recovery. Tumors were staged according to the sixth tumor–node–metastasis (TNM) classification of the International Union Against Cancer (UICC) based on the histological findings of the surgical specimens. Adherence to oncologic surgical principles was evaluated by analyzing the distal margin and number of lymph nodes harvested.

Operative procedure

All patients underwent bowel preparation, except those who presented with bowel obstruction. Antibiotic prophylaxis consisted of 1 g cefmetazole sodium administered intraoperatively every 3 h. The surgical team comprised an operating surgeon, an assistant surgeon, and an endoscopist. We used mainly a monopolar electrocautery for dissection and used laparosonic coagulating shears (LCS) only in specific fields since we believe that electrocautery is useful for dissecting tissues in layers. The patients were put into the extended Lloyd–Davis position, with the legs not angled too steeply, in order to prevent restriction of the surgical field. The umbilical port for the telescope was inserted using the open technique, and pneumoperitoneum was established by insufflation of carbon dioxide (8–10 mmHg). While viewing the laparoscopic image thus obtained, one port each (5–12 mm in diameter) was inserted in the left upper, left lower, right upper, and right lower abdominal quadrants. The patients were then positioned in the reverse Trendelenburg position and turned to their right. We used the mediolateral approach, beginning with central mobilization of the inferior mesenteric vessels and systematic identification of the left ureter. TME was performed in all patients, except in those in whom the tumor was confined to the upper part of the rectum; in this case, tumor-specific mesorectal excision (TSME) was performed. The Denonvilliers' fascia was preserved, except in the case of rectal cancer involving the anterior rectal wall. In women, the uterus was pulled toward the abdominal wall by using sutures. A good laparoscopic view of the surgical field and countertraction provided by the assistant surgeon enabled the identification of the dissection layers. This helped prevent injury to the neurovascular bundles and preserve the hypogastric nerves and pelvic plexus. Except in the case of very low rectal cancer, rectal transection was performed using an endoscopic linear stapler inserted through the right lower port, and the rectal specimen was exteriorized through a small incision in the left lower abdominal quadrant. A double-stapled coloanal anastomosis was created using a circular stapler, and the anastomotic rings were inspected for integrity. In the case of very low rectal cancer, transanal intersphincteric resection and hand-sewn anastomosis were performed to transect the lower rectum and obtain a longer distal margin than that obtained by intracorporeally transecting the rectum at the upper portion of the anorectal ring. A temporary ileostomy was constructed in patients who underwent preoperative radiotherapy or transanal hand-sewn anastomosis.

Training program

It is important for resident surgeons to operate on a sufficient number of patients and gradually master laparoscopic procedures. Our systematic training program for laparoscopic surgery was structured to enable stepwise acquisition of laparoscopic skills as follows:

1. In the first step, resident surgeons are required to act as endoscopists in at least 20 LCRs in order to learn the essentials of the standardized techniques used in LCRs. The surgeons also perform other basic laparoscopic procedures (e.g., cholecystectomy, stoma creation, omental patch repair for gastroduodenal perforation).
2. In the next step, the resident surgeons are required to act as operating surgeons and perform laparoscopic sigmoid colectomy and ileocecal resection and develop basic laparoscopic skills (prior experience in open colon surgery not required).
3. Thereafter, the resident surgeons perform laparoscopic hemicolectomy (both sides) and laparoscopic transverse colectomy and acquire advanced laparoscopic skills.
4. Laparoscopic surgery for rectal cancer, especially LLAR or laparoscopic abdominoperineal resection, is the most demanding among LCRs. It is therefore the last procedure that the resident surgeons perform, after they have acted as operating surgeons in at least 30 other LCRs and as endoscopists or assistant surgeons in more than 30 LCRs, including TME. The resident surgeons then perform about the same number (30) of laparoscopic procedures other than LCRs.

Resident surgeons are also encouraged to view a collection of video recordings of laparoscopic procedures. This enhances the effectiveness and quality of surgical education.

Quality assurance in the surgical procedures is very important throughout the training process. In order to maintain the quality of LCRs performed by resident surgeons, our systematic training program emphasizes the following principles:

1. In order to ensure surgical quality, we select the operating and assistant surgeons after considering the surgical skills of the expert and resident surgeons and the technical difficulty associated with patient-related factors, including adiposity, gender, tumor stage, tumor size, and tumor location.
2. Expert surgeons assist resident surgeons during the operation; they prepare the surgical field and provide continuous traction. Thus, the resident surgeons can obtain accurate magnification and correctly identify all small and important anatomical structures, even a narrow pelvis. They can also learn the techniques of precise anatomical dissection.
3. We ensure that all surgeons use the standardized techniques for LCRs. In general, it is accepted that during conventional open colorectal surgery, senior surgeons, acting as assistant surgeons, can control the quality of surgery performed by resident surgeons. However, this type of quality control is difficult during LCRs since the operating and assistant surgeons play completely different roles. The assistant surgeon cannot physically help the operating surgeon since the assistant surgeon is always occupied in developing the surgical field. Therefore, the use of standardized techniques is essential to maintain the quality of LCRs performed by resident surgeons. Standardization of the procedures also helps the expert surgeons to teach and the resident surgeons to easily understand the details of the surgical procedure.

Statistical analysis

All analyses were performed on an intention-to-treat basis, and the assessment included the patients in whom conversion to open LAR was required. Statistical analysis was performed using Student's t test and Welch's t test for continuous data and Fisher's exact test for categorical data. Continuous variables are expressed in terms of the mean (range). All statistical tests were two-sided, and differences were considered significant when $p < 0.05$.

Results

Patient demographics, tumor characteristics, and operative procedure

Between February 2001 and March 2008, 142 patients underwent LLAR for rectal cancer at Kyoto Medical Center. We excluded five patients who underwent LLAR and other major procedures simultaneously. In the E-E group, one patient underwent laparoscopic transverse colectomy and one underwent laparoscopic distal gastrectomy, in addition to LLAR. In the I-R group, two patients underwent hepatic metastasectomy and one underwent open distal gastrectomy, in addition to LLAR. We examined the remaining 137 patients: 75 with intraperitoneal rectal cancer (40 in the I-E group and 35 in the I-R group) and 62 with extraperitoneal rectal cancer (51 in the E-E group and 11 in the E-R group). Most of the LLARs in the I-E and E-E groups were performed by YS, HK, or TY, who are proficient in performing LCRs and have more than 12 years of experience. LLARs in the I-R and E-R groups

Table 1 Patient demographics, tumor characteristics, and operative procedure

	Intraperitoneal ($n = 75$)		p value	Extraperitoneal ($n = 62$)		p value
	I-E group ($n = 40$)	I-R group ($n = 35$)		E-E group ($n = 51$)	E-R group ($n = 11$)	
Age (years) (range)	62.7 (44–86)	69.7 (41–93)	0.005	62.0 (37–84)	64.2 (26–80)	NS
Gender [n (%)]						
Male	24 (60)	21 (60)	NS	27 (52.9)	5 (45.4)	NS
Female	16 (40)	14 (40)		24 (47.1)	6 (54.5)	
Previous abdominal surgery [n (%)]	4 (10)	9 (25.7)	NS	6 (11.8)	2 (18.2)	NS
Tumor size (mm) (range)	50.4 (10–90)	42.4 (0–90)	NS	37.5 (0–80)	35.3 (18–65)	NS
TNM stage [n (%)]						
0	3 (7.5)	0	NS	5 (9.8)	2 (18.2)	NS
I	7 (17.5)	12 (34.3)	NS	21 (41.2)	3 (27.3)	NS
II	8 (20)	7 (20)	NS	11 (21.6)	0	NS
III	16 (40)	10 (28.6)	NS	12 (23.5)	3 (27.3)	NS
IV	6 (15)	6 (17.1)	NS	2 (3.9)	3 (27.3)	0.049
LAR with double-stapling technique	40	35	NS	43 (84.3)	9 (81.8)	NS
LAR with transanal hand-sewn anastomosis	0	0	NS	8 (15.7)	2 (18.2)	NS
Diverting ileostomy	0	2 (5.7)	NS	13 (25.5)	2 (18.2)	NS

were performed by six resident surgeons with 2–7 years of experience; of these resident surgeons, three had no prior experience in open surgery and three had experience in open surgery and basic laparoscopic surgery.

Patient demographics, tumor characteristics including pathological staging; and operative procedure undertaken are listed in Table 1. Expert surgeons operated on a significantly larger number of patients with extraperitoneal rectal cancer than resident surgeons ($p < 0.001$). The patients were significantly younger in the I-E group than in the I-R group. The incidence of stage IV tumors was significantly higher in the E-R group than in the E-E group. No significant differences were observed between the I-E and I-R groups or between the E-E and E-R groups with regard to gender, previous abdominal surgery, tumor size, and operative procedure.

Operative time, blood loss, conversion to open LAR, and intraoperative and postoperative complications

The operative details and complications are listed in Table 2. The mean operative time was significantly shorter in the E-E group than in the E-R group, while it was similar in the I-E and I-R groups. The mean blood loss was less in the E-E group than in the E-R group, but the difference was not significant ($p = 0.45$). The incidences of conversion to open LAR, intraoperative complications, and postoperative complications, including anastomotic leakage, were similar in the I-E and I-R groups and in the E-E and E-R groups.

Of the eight intraoperative complications encountered, six were due to equipment failure, with similar incidence in the I-E and I-R groups and in the E-E and E-R groups. Of the six patients who developed complications because of equipment failure, two required conversion to open LAR and two developed anastomotic leakage. The incidence rates of conversion to open LAR and anastomotic leakage were significantly higher among the patients with complications due to equipment failure than among those without such complications [conversion to open LAR: 33.3% (2 of 6 patients) vs. 4.6% (6 of 131 patients); odds ratio (OR) = 10.417; 95% confidence interval (CI) = 1.880–61.092; Fisher's exact test, $p = 0.040$; and anastomotic leakage: 33.3% (two of six patients) vs. 4.6% (six of 131 patients); OR = 10.417; 95% CI = 1.880–61.092; Fisher's exact test, $p = 0.040$). The remaining two intraoperative complications were tumor perforation during the extraction of a large tumor through the minilaparotomy incision and bowel injury during the insertion of the first umbilical port. Most of the postoperative complications were managed conservatively; however, five patients required surgical intervention. Reoperation was performed in one patient in the I-E group because of anastomotic leakage, in one patient in the I-R group because of perforation of the small intestine, in two patients in the E-E group because of wound dehiscence and anastomotic leakage, and in one patient in the E-R group because of formation of abdominal abscess. There were no deaths in any group. The causes of conversion to open LAR are listed in Table 3.

Table 2 Operative details, conversion to open surgery, and intraoperative and postoperative complications

	Intraperitoneal ($n = 75$)		p value	Extraperitoneal ($n = 62$)		p value
	I-E group ($n = 40$)	I-R group ($n = 35$)		E-E group ($n = 51$)	E-R group ($n = 11$)	
Operative time (min) (range)	280 (156–429)	309 (195–542)	NS	301 (160–615)	357 (240–558)	0.047
Blood loss (ml) (range)	108 (0–1130)	80 (0–700)	NS	109 (0–650)	163 (0–700)	NS
Intraoperative complications [n (%)]	3 (7.5)	2 (5.7)	NS	2 (3.9)	1 (9.1)	NS
Dehiscence of the rectal stump (malfunction of endoscopic stapler) [n (%)]	2 (5.0)	2 (5.7)	NS	1 (2.0)	0 (0)	NS
Drawbacks with circular stapler	0 (0)	0 (0)	NS	1 (2.0)	0 (0)	NS
Bowel injury [n (%)]	0 (0)	0 (0)	NS	0 (0)	1 (9.1)	NS
Tumor perforation [n (%)]	1 (2.5)	0 (0)	NS	0 (0)	0 (0)	NS
Conversion [n (%)]	3 (7.5)	1 (2.9)	NS	3 (5.9)	1 (9.1)	NS
Postoperative complications [n (%)]	6 (15.0)	5 (14.3)	NS	10 (19.6)	2 (18.2)	NS
Anastomotic leakage [n (%)]	3 (7.5)	1 (2.9)	NS	3 (5.9)	1 (9.1)	NS
Wound infection [n (%)]	1 (2.5)	2 (5.7)	NS	3 (5.9)	0 (0)	NS
Bowel obstruction [n (%)]	0 (0)	1 (2.9)	NS	3 (5.9)	0 (0)	NS
Intra-abdominal abscess [n (%)]	0 (0)	0 (0)	NS	0 (0)	1 (9.1)	NS
Others [n (%)]	2 (5.0)	1 (2.9)	NS	1 (2.0)	0 (0)	NS
Reoperation [n (%)]	1 (2.5)	1 (2.9)	NS	2 (3.9)	1 (9.1)	NS
Mortality [n (%)]	0 (0)	0 (0)	NS	0 (0)	0 (0)	NS

Table 3 Causes of conversion to open surgery

	Intraperitoneal ($n = 75$)		Extraperitoneal ($n = 62$)	
	I-E group ($n = 40$)	I-R group ($n = 35$)	E-E group ($n = 51$)	E-R group ($n = 11$)
Dehiscence of the rectal stump (endoscopic stapler failure)	1	0	1	0
Involvement of the bladder	1	0	0	0
Involvement of the lateral pelvic plexus	0	0	0	1
Massive lymph node swelling	0	1	0	0
Extensive adhesions associated with multiple previous laparotomies	0		1	0
Severe endometriosis	1	0	0	0
Morbid obesity	0	0	1	0

Bowel recovery, distal margin, and number of lymph nodes harvested

The bowel function and oncological parameters are listed in Table 4. No significant differences were observed between the I-E and I-R groups or between the E-E and E-R groups with regard to the time to the passage of the first flatus and feces. The time to resumption of diet was significantly longer in the I-E group than in the I-R group. The mean number of lymph nodes harvested and the mean distal margin were similar in the I-E and I-R groups and in the E-E and E-R groups. One positive resection margin was identified in the I-R group in a patient with hypogastric nerve involvement and massive lymph node involvement.

Discussion

While laparoscopic surgery is the standard treatment for colon cancer, it is not yet popular for the treatment of rectal cancer; this is because laparoscopic rectal surgery is technically challenging and is associated with some disadvantages such as long operative time [1, 2, 4] and increased rate of positive surgical margins [9]. Even during open surgery in the deep and narrow pelvic region, it is very difficult to maintain a clear surgical field, precisely identify anatomical structures, and accurately perform rectal mobilization and excision while preserving urogenital functions. It is considered that laparoscopic surgery takes a longer time to learn than open surgery and that laparoscopic training should be initiated after open surgical procedures have been

Table 4 Bowel recovery, distal margin, and number of lymph nodes harvested

	Intraperitoneal ($n = 75$)		p value	Extraperitoneal ($n = 62$)		p value
	I-E group ($n = 40$)	I-R group ($n = 35$)		E-E group ($n = 51$)	E-R group ($n = 11$)	
Days to first flatus (range)	1.78 (0–6)	1.60 (0–5)	NS	1.65 (0–10)	2.09 (1–3)	NS
Days to first feces (range)	2.23 (0–8)	2.31 (0–8)	NS	2.33 (0–10)	3.36 (0–8)	NS
Days to diet (range)	3.40 (1–11)	2.37 (1–6)	0.024	3.49 (1–13)	3.90 (1–8)	NS
Lymph nodes harvested [n (range)]	12.7 (3–31)	14.7 (1–45)	NS	11.3 (2–41)	13.6 (2–36)	NS
Distal margin (mm) (range)	42.9 (15–110)	49.7 (15–180)	NS	22.8 (5–50)	19.7 (10–35)	NS
Positive resection margin [n (%)]	0 (0)	1 (2.9)	NS	0 (0)	0 (0)	NS

learned. Furthermore, suitable training programs for advanced laparoscopic procedures have been lacking [10–12] and have been studied in only a few reports [13]. We developed a systematic training program that offers sufficient experience in LCRs to resident surgeons without prior experience in open colorectal surgery and enables them to acquire the skills required for performing LLAR for rectal cancer. The present study was designed to evaluate the safety and feasibility of our systematic training program.

The demographic characteristics of the patients operated on by expert surgeons differed from those of the patients operated on by resident surgeons. Expert surgeons operated on a significantly larger number of patients with extraperitoneal rectal cancer than resident surgeons ($p < 0.001$). The difference may be partly explained by our policy for selecting the operating surgeons. LLAR for low rectal cancer is considered to be more demanding than that for high rectal cancer and, therefore, expert surgeons might be preferred as operating surgeons for LLAR for extraperitoneal rectal cancer. For the same reason, we analyzed the outcomes of LLARs for intraperitoneal rectal cancer and those for extraperitoneal rectal cancer separately.

The reason for the difference in the age of the patients between the I-E and I-R groups is difficult to explain. Actually, some authors have reported that laparoscopic surgery in elderly patients is not especially associated with high morbidity [14, 15], and we did not consider the age of the patients when assigning them to either group. The larger number of stage IV patients in the E-R group than in the E-E group may also be explained by our policy for selecting the operating surgeons. In LLARs for stage IV tumors, surgeons do not need to adhere to oncologic radicality so the selection of resident surgeons is easy.

All surgical outcomes, including operative time, blood loss, conversion to open LAR, and complications, were similar in the I-E and I-R groups. The operative time was significantly longer in the E-R group than in the E-E group; however, this not associated with a compromise in patient care. No significant differences were observed between the E-E and E-R groups with regard to blood loss, rate of conversion to open LAR, incidence of intraoperative complications, and incidence of postoperative complications, including anastomotic leakage. Furthermore, the values of the above parameters were satisfactory when compared with those reported in other series [1–4, 6, 9, 16–25]. The resident surgeons needed a longer operative time than the expert surgeons for LLARs for extraperitoneal rectal cancer but not for LLARs for intraperitoneal rectal cancer. This might be because LLAR for extraperitoneal rectal cancer is more demanding and can reveal unsatisfactory surgical skills of resident surgeons than that for intraperitoneal rectal cancer.

The most common intraoperative complication in all the groups was failure of the endoscopic linear stapler or circular stapler; the incidence of this complication did not differ among the four groups. In this study, intraoperative equipment failure was associated with increased risk of conversion to open LAR and anastomotic leakage. This finding reinforces the importance of the appropriate use and selection of surgical devices.

The longer time to resumption of diet in the I-E group than in the I-R group may be partly associated with the higher incidence of anastomotic leakage in the I-E group than in the I-R group (the difference was not statistically significant). The other outcomes with regard to time to bowel recovery were similar in the I-E and I-R groups and in the E-E and E-R groups, and well within the previously reported range [1–5, 9, 18, 19, 21, 22].

The mean number of lymph nodes harvested was similar in the I-E and I-R groups and in the E-E and E-R groups and was more than the adequate number, suggesting that extensive lymphadenectomy was performed. The mean distal margin was similar in the I-E and I-R groups and in the E-E and E-R groups, and its value almost agrees with that reported in other series [1, 2, 16, 18–25], suggesting that wide dissection and resection were performed.

A higher incidence of positive resection margins after laparoscopic surgery for rectal cancer than that after open surgery has been reported and may result in a higher local recurrence rate [9]. In this study, only one positive resection margin was identified in the I-R group. In all the

groups, the accepted oncologic surgical principles were adhered to during LLARs.

The results of this study confirm the findings of other studies regarding training programs for open surgical procedures for colorectal cancer [26, 27] and for laparoscopic surgical procedures including laparoscopic colectomy [28–30]. The short-term surgical and functional outcomes in the I-R and E-R groups were almost as good as those in the I-E and E-E groups, respectively, and were quite satisfactory, although the expert surgeons obtained significantly better results with respect to operative time in LLARs for extraperitoneal rectal cancer. Furthermore, oncologic requirements were fulfilled in all the groups. This study analyzed only the short-term outcomes of LLARs; long-term follow-up is required to ensure that oncological procedures during LLAR are not compromised in any group. Nonetheless, we believe that this study demonstrates the safety and feasibility of our systematic program for training resident surgeons to perform LLAR for rectal cancer.

Our systematic training program has a unique concept regarding the suitable timing for the introduction of advanced laparoscopic procedures during residency. Because of the steep learning curve for LCR, it is considered that it takes longer to learn laparoscopic surgery, especially LLAR, than to learn open surgery. Moreover, laparoscopic training is commonly initiated after completion of training for open surgery. In this study we have shown that prior experience with open surgery is not a prerequisite for training in laparoscopic surgery; furthermore, through sufficient experience, resident surgeons can acquire the skills required for performing LLAR early in their training period. We consider that with regard to the training of resident surgeons, laparoscopic surgery presents some advantages over open surgery: a magnified image of the surgical field can be obtained even in the case of a deep and narrow pelvis, and everyone involved in the surgery can view the surgical field and learn the procedure from digital records. In addition, in our systematic training program, the use of standardized techniques is emphasized and expert surgeons assist resident surgeons in order to ensure effective education and procedural safety.

There is limited evidence regarding the oncologic adequacy of LLAR for rectal cancer; however, an increasing number of institutions actually employ LLAR for the treatment of rectal cancer. Therefore, it is necessary that the quality of LLAR is ensured in each institution. It is paramount that today's general surgery residency programs incorporate training for advanced laparoscopic procedures into their curriculum and that surgical trainees are given sufficient experience in laparoscopic surgery in a properly structured training program. In summary, the present study suggests that the introduction of LLAR for rectal cancer early during residency is a feasible training concept.

Disclosures Drs. Satoshi Ogiso, Takashi Yamaguchi, Hiroaki Hata, Hiroya Kuroyanagi, and Yashiharu Sakai have no conflicts of interest or financial ties to disclose.

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REVIEW

Impact of metastatic lymph node ratio in node-positive colorectal cancer

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Abstract

Colorectal cancer (CRC) is one of the most common malignant diseases in the world. Presently, the most widely used staging system for CRC is the tumor nodes metastasis classification system, which classifies patients into prognostic groups according to the depth of the primary tumor, presence of regional lymph node (LN) metastases, and evidence of distant metastatic spread. The number of LNs with confirmed metastasis is related to the severity of the disease, but this number depends on the number of LNs retrieved, which varies depending on patient age, tumor grade, surgical extent, and tumor site. Numerous studies and a recent structured review have demonstrated associated improvements in the survival of CRC patients with increasing numbers of LNs retrieved for examination. Hence, the impact of lymph node ratio (LNR), defined as the number of metastatic LNs divided by the number of LNs retrieved, has been investigated in various malignancies, including CRC. In this editorial, we review the literature demonstrating the clinicopathological significance of LNR in CRC patients. Some reports have indicated the advantage of considering the LNR compared to the number of LNs retrieved and/or LN status. When the LNR is taken into consideration for survival analysis, the number of LNs retrieved and/or the LN status is not always found to be a prognostic factor. The cut-off points for LNRs were proposed in numerous studies. However, optimal thresholds for LNRs have not yet received consensus. It is still unclear whether the LNR has more prognostic validity than N stage. For all these reasons, the potential advantages of LNRs in the staging system should be investigated in large prospective data sets.

Key words: Lymph node ratio; Lymph node; Colorectal cancer; Prognostic factor; Tumor nodes metastasis stage

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INTRODUCTION

Colorectal cancer (CRC) is among the most common malignant diseases in the Western world, whereas cancers of the upper gastrointestinal tract (esophagus and stomach) and liver are more predominant in the Eastern world. However, many Asian countries, including Japan, have experienced a

2-4-fold increase in the frequency of CRC during the past few decades[1,2].

The principal feature of a cancer staging system is its ability to provide an accurate prognosis and to guide appropriate clinical decisions regarding postoperative management and follow-up. In 1932, Dukes[3] developed a classification system for rectal cancer. This system classified cancers on the basis of tumor extension and lymph node (LN) status. This classification system is still being widely used for the prognostic evaluation of patients who undergo surgery for CRC. Subsequently, numerous modifications have been proposed to improve the prognostic predictive ability of the original Dukes classification[4-6]. Metastasis to regional LNs is an important prognostic factor and is used for clinical decision-making regarding the selection of the most appropriate cancer treatment[7-9]. Currently, the most widely used staging system is the tumor nodes metastasis (TNM) classification system[10]. The TNM staging system classifies patients into prognostic groups according to the depth of the primary tumor, presence of regional LN metastases, and evidence of distant metastatic spread. Regional LN status (N) is determined on the basis of the number of positive LNs retrieved and is classified as follows: no regional LN metastasis (N0), metastasis in 1-3 regional LNs (N1), and metastasis in 4 or more regional LNs (N2).

In Japan, the Japanese classification of colorectal carcinoma has been widely used[11]. This staging system classifies patients into different stages according to the depth of tumor invasion, LN metastasis, and hepatic, peritoneal, and extrahepatic distant metastasis, with extrahepatic distant metastasis not including hepatic and/or peritoneal metastasis. LN metastasis beyond the regional LNs is classified as distant metastasis. Treatment varies according to the progression of distant metastases. Aggressive resection for hepatic and/or peritoneal metastasis obtains a favorable survival rate.

LN status is determined on the basis of the number and location of positive LNs retrieved and is classified as follows: no evidence of LN metastasis (N0), metastasis in 1-3 pericolic/perirectal or intermediate LNs (N1), metastasis in 4 or more pericolic/perirectal or intermediate LNs (N2), and metastasis in the main LNs at the root of the artery or lateral LNs (N3). Some researchers, however, believe that the TNM staging system may not result in optimal staging and have proposed alternative LN parameters.

TOTAL NUMBER OF DISSECTED LYMPH NODES AND N STAGE

For correct nodal staging, it is necessary to thoroughly examine postoperative specimens and obtain an adequate number of nodes. At present, specimens are fixed for histologic study and LNs are usually obtained visually or by palpation by a pathologist. The fat-clearance technique has been shown to increase the accuracy of LNs harvested in surgical specimens compared with the manual dissection method[12-14]. The former method has enabled the upstaging of more than 50% of stage II cases to stage III, by allowing the identification and examination of previously undetected LNs[15]. Serial node dissection, *ex vivo* nodal mapping, and immunohistochemical staining have also been proposed as novel and viable techniques to improve LN evaluation[16]. However, these tests are time-consuming and expensive and are thus used infrequently. The American College of Pathologists has issued guidelines that advocate the use of additional techniques on resected colorectal specimens if fewer than 12 nodes are identifiable using conventional methods[17]. This may be a valid method for ensuring the judicious use of special techniques.

Ratto *et al*[18] investigated the different pathologic methods for LN identification in CRC patients. In Group 1, the specimens were fixed "*en bloc*" and a pathologist examined the specimens and identified the LNs visually and by palpation. In Group 2, the mesentery of the excised specimen was dissected away from the bowel. According to the site, the mesentery was divided into 3 specimen segments and fixed. After fixation, the pathologist identified the LNs. The mean number ± standard deviation of LNs found per patient was 29.6 ± 16.7 in Group 2, which was significantly higher than that detected in Group 1 (11.3 ± 5.8, $P < 0.01$). The mean number of involved LNs diagnosed in Group 2 (5.9 ± 11.5) was higher than that in Group 1 (2.9 ± 2.4, $P = 0.002$). In Group 2, the metastatic rate (37.5%) was significantly higher than that of Group 1 (30.2%, $P < 0.05$); similar characteristics were demonstrated while stratifying the patients according to the tumor site. However, the metastatic incidences were analogous in the 2 groups (Group 1, 7.7%; Group 2, 7.4%; $P = 0.3$).

Numerous studies and a recent structured review have demonstrated an improvement in the overall survival (OS) and/or disease-free survival (DFS) of CRC patients with increasing numbers of LNs retrieved for examination; such improvement has also been observed in patients with known LN-positive disease[19-28]. However, a population-based analysis revealed that the median number of LNs examined was 9 and that only 37% of patients with CRC received adequate LN evaluation (i.e. at least 12 LNs examined)[29]. This could be attributed to various patient-, tumor-, surgeon-, and/or pathologist-related variables. The two potentially modifiable variables are the completeness of LN evaluation by the pathologists conducting the examinations and the adequacy of the surgical resection method[30]. It is very important to establish the minimum number of LNs required for an acceptable accuracy in classifying a tumor as LN negative. The Working Party Report to the World Congress of Gastroenterology recommended that a minimum number of 12 LNs should be examined, although it was not stated how this figure was obtained[31]. Nonetheless, the agenda for adequate LN evaluation is still debatable. Recently, published studies assessing the number of LNs resected in CRC have reported wide variation in the extent of resection. Although these studies demonstrate a prognostic association between the number of LNs examined and survival, the cut-off values vary widely; i.e. from 6 to 40[19-21,24,32,33]. Current

guidelines established by the American Joint Committee on Cancer recommend the assessment of 12 or more nodes for accurate staging[9].

The number of resected LNs is important for staging and can be accomplished by adequate surgical resection and diligent pathologic examination. Despite the efforts of surgeons and pathologists, there are several other factors that could influence LN retrieval. It is generally considered that the right side of the colon is associated with a higher number of LNs examined than the left side of the colon and rectum[25,29,32,34]. This difference can be attributed to the fact that larger pieces of mesenteric lymphatic stations can be excised during right colectomy than during left colectomy[32]. Many rectal cancer patients receive preoperative radiotherapy, with or without chemotherapy. This neoadjuvant therapy has been shown to result in a significant decrease in both the size and number of LNs available for examination after resection[29,35]. In addition, older age and obesity may reduce the number of LNs retrieved[29,32,36]. Also, the number of LNs that can be retrieved may also depend on the immune response of a patient as the size and morphology of LNs are modified by immune responses[37,38].

LYMPH NODE RATIO

Recent studies on malignancies emphasize the importance of the number of LNs examined to establish a prognosis. There are two opposing views on the importance of lymphadenectomy in determining survival; some investigators believe that a complete lymphadenectomy has a therapeutic benefit, whereas others believe that it simply provides more accurate staging[39]. The number of LNs with confirmed metastasis is not only related to the severity of the disease, but also depends on the number of LNs retrieved, which varies depending on patient age, tumor grade, surgical extent, and tumor site. The impact of the lymph node ratio (LNR), which is the number of metastatic LNs divided by the number of retrieved LNs for each patient, was first investigated in gastric cancers, with reference to its application as a novel prognostic factor for identifying prognostic subgroups among gastric cancer patients with LN metastasis[40]. In this study, they evaluated the prognostic value of ratio groupings of LNR = 0.01-0.15, LNR = 0.16-0.30, and LNR > 0.31 in 401 patients with stage Ⅲ and Ⅳ gastric cancer. Multivariate survival analysis using Cox's proportional hazard model was applied to 3 forms of N status (LNR, N stage, and number of metastatic LNs). Among these 3 variables, LNR and N stage were independent prognostic factors [relative risk (RR), 2.4294 and 2.1150, $P = 0.0001$ and 0.0048, respectively]. However, the number of metastatic LNs was not an independent prognostic factor (RR, 0.6722, $P = 0.1092$). Subsequently, many studies have evaluated LNR in various malignancies, including gastric[41,42], esophageal[43], pancreas[44], breast[45,46], and bladder cancers[47]. However, to date, there have been no formal guidelines indicating that LNR should be used as an alternative to N stage.

LNR IN CRC

Surgical clearance and pathologic examination of the resected LNs has long been a standard component of operable CRC management. Complete LN dissection is still thought to provide the most accurate information regarding the disease when positive nodes are identified. LNR, which takes into account the degree of LN dissection, is an alternative to determining the absolute number of positive LNs. Indeed, experienced teams often perform meticulous and extensive LN dissection, which increases the probability of finding nodes. Therefore, patients with inadequate LN resection could receive less efficient adjuvant treatment[48]. There is a potential for stage migration when an inadequate number of LNs is harvested[22]. With respect to emerging diagnostic techniques, the concept of stage migration was first described by Feinstein *et al*[49] in 1985 and was termed as the Will Rogers Phenomenon.

Several studies have investigated the LNR in CRC [22,26-28,34,48,50-61] (Table 1). Berger *et al*[22] were the first to investigate the relationship between LNR and survival in patients with colon cancer. Of the 3411 assessable patients, 648 (19%) were N0, 1857 (54%) were N1, and 906 (27%) were N2. The mean number of retrieved LNs was 13. In a multivariate analysis, LNR was found to be a significant factor for OS, DFS, and cancer-specific survival (CSS) in patients in whom 10-15 LNs and more than 15 LNs were removed, but not for patients in whom less than 10 LNs were removed.

De Ridder *et al*[48] directly compared the TNM staging system to the LNR-based staging. The median number of retrieved LNs was 10. The prognostic separation using LNRs was 31% and that using N stages was 26%.

Wang *et al*[27,54] reported on 24477 stage Ⅲ colon cancer cases. In only 7469 (30.5%) patients, more than 15 LNs could be harvested from the specimen. They categorized the patients into 4 groups; i.e. LNR1 to LNR4, on the basis of the cut-off points 1/14, 1/4, and 1/2, respectively. There was no difference in the survival rate among the stage ⅢA patients in the LNR1 to LNR4 groups ($P = 0.08$). The 5-year survival rate of the stage ⅢB patients in the LNR1, LNR2, LNR3, and LNR4 groups was 63.5%, 54.7%, 44.4%, and 34.2%, respectively ($P < 0.0001$). The 5-year survival rate of the stage ⅢC patients with LNR2, LNR3, and LNR4 was 49.6%, 41.7%, and 25.2%, respectively ($P < 0.0001$). LNR was an independent predictor of survival after adjusting for patient age, tumor size, tumor grade, race, number of positive LNs, and total number of LNs harvested [RR, 2.30; 95% confidence interval (CI), 2.08-2.55].

In a single center analysis, Rosenberg *et al*[26] reported the prognostic impact of LNRs in 3026 CRC patients. In all, 1763 colon and 1263 rectal carcinomas were documented. The mean numbers of retrieved and metastatic LNs for each patient were 18.3 and 2.6, respectively. The mean LNR was 0.14. In multivariate analysis, both LNR and N stage were found to be independent prog-

Table 1 Lymph node ratio (LNR) in colorectal cancer

Author, year	[Reference]	No. of patients	Selection of patients	Cut-off of LNR	5-year overall survival (%)	Uni *P* value	Multi *P* value	HR (95% CI)
Berger *et al*, 2005	[22]	3411	Stage II and III colon cancer	< 0.05	79	< 0.0001	[1]NS[a]	-
				0.05-0.19	73		[1]< 0.0001[b]	[1]3.87 (NA)[b]
				0.2-0.39	63		[1]< 0.0001[c]	[1]12.43 (NA)[c]
				0.4-1.0	52			
De Ridder *et al*, 2006	[46]	26181	Node-positive colon cancer	-0.4	56	-	< 0.0001	-
				0.4-	25			
Schumacher *et al*, 2007	[50]	232	Non-stage IV colon cancer	< 0.08	-	< 0.05	-	-
				0.08 ≤	-			
Lee *et al*, 2007	[51]	201	Stage III colon cancer	0.01-0.11	83.6[d]	< 0.0001	< 0.0001	1
				0.12-0.24	61.1[d]			2.973 (1.407-6.280)
				0.25-0.92	20[d]			8.362 (3.739-18.704)
Wang *et al*, 2008, 2009	[27,54]	24477	Stage III colon cancer	< 1/14	64.8	< 0.0001	[1]< 0.0001	[1]2.30 (2.083-2.545)
				1/14 ≤ - < 0.25	56.2			
				0.25 ≤ - 0.50	45.1			
				0.50 ≤ - ≤ 1.0	29.6			
Rosenberg *et al*, 2008	[26]	3026	Colorectal cancer	0	87.1	< 0.001	< 0.001	1 (NA)
				0.01-0.17	60.6			1.92 (NA)
				0.18-0.41	34.4			2.92 (NA)
				0.42-0.69	17.6			3.62 (NA)
				0.70 ≤	5.3			4.31 (NA)
Peng *et al*, 2008	[52]	318	Node-positive rectal cancer	< 0.14	72.19	0.002	[1]0.003	[1]3.11 (1.47-6.58)
				0.14-0.49	61.92			
				0.5-1	38.47			
Peschaud *et al*, 2008	[53]	307	Rectal cancer	0	89[e]	0.0013	[1]0.0003	[1]1.019 (1.009-1.029)
				0.01-0.07	92[e]			
				0.07-0.2	71[e]			
				0.2 <	67[e]			
Derwinger *et al*, 2008	[55]	136	Stage IV colorectal cancer	0-0.15	708 d[f]	< 0.0049	[1]< 0.05[g]	2.1 (1.3-3.6)[g]
				0.16-0.65	438 d[f]			
				0.66-1	277 d[f]			
Derwinger *et al*, 2008	[56]	265	Stage III colon cancer	0-0.125	80[h]	< 0.001	[1]< 0.0002	[1]10.6 (3.2-31.8)
				0.126-0.266	-			
				0.267-0.450	-			
				0.451-1	29[h]			
Vather *et al*, 2009	[57]	2364	Stage III colon cancer	Lowest group	55-60	< 0.0001	-	-
				Higher group	10-20			
Chin *et al*, 2009	[34]	490	Stage III colon cancer (LN ≥ 12)	≤ 0.4	66.7[d]	< 0.0001		1
				0.4 < ≤ 0.7	35.1[d]		0.001	2.298 (1.384-3.815)
				0.7 <	0[d]		< 0.001	7.407 (3.153-17.397)
Vaccaro *et al*, 2009	[61]	362	Stage III colon cancer	< 0.25	64.9	< 0.0001	0.005	1
				0.25 ≤	38.3			2.3 (1.3-4.1)
Park *et al*, 2009	[28]	318	Stage III colon cancer	< 0.059	83.6[h]	0.0002	-	-
				0.059-0.23	71.1[h]			
				0.23 <	55[h]			
Priolli *et al*, 2009	[58]	113	Colorectal cancer	0	More than 80	0.03	[1]0.003	[1]8.575 (NA)
				0.01-0.2	67.6			
				0.21 ≤	37.5			
Moug *et al*, 2009	[59]	295	Colorectal cancer	< 0.05	-	< 0.001	[1]< 0.001[i]	[1]11.65 (5.00-27.15)[i]
				0.05-0.19	-		[1]< 0.001[i]	[1]13.40 (3.64-49.10)[i]
				0.20-0.39	-			
				0.40-1.00	-			
Kim *et al*, 2009	[60]	232	Stage III rectal cancer	≤ 0.1	89	< 0.001		1
				0.1 < - ≤ 0.2	67		0.623	1.260 (0.501-3.173)
				0.2 < - ≤ 0.4	64		0.0047	2.435 (1.012-5.862)
				0. 4 <	50		0.005	3.701 (1.493-9.178)

Uni: Univariate analysis; Multi: Multivariate analysis; HR: Hazard ratio; 95% CI: 95% Confidence interval; NS: Not significant; NA: Not available; LN, Lymph node; [1]In multivariate analysis, LNR was considered as a continuous variable; [a]In patients with LN < 10; [b]In patients with LN 10-15; [c]In patients with LN > 15; [d]5-year disease-free survival; [e]3-year overall survival; [f]Median survival in days; [g]In patients with LN ≥ 12; [h]3-year disease-free survival; [i]In colon cancer patients; [j]In rectal cancer patients.

nostic factors. LNR had a better prognostic value than the N stage ($P < 0.05$). The analysis of a subgroup of patients classified into colon and rectal cancer patients confirmed the identified LNRs as an independent prognostic factor ($P < 0.001$).

Peng *et al*[52] demonstrated for the first time the relation-

ship between LNRs and survival rates in rectal cancer patients. The average numbers of retrieved and metastatic LNs for each patient were 12 and 3.8, respectively. The mean LNR was 0.34. Multivariate analysis revealed that LNR was an independent risk factor for local recurrence rate, DFS, and OS; the hazard ratios (HRs) were 8.50 (95% CI, 2.25-32.03; $P = 0.002$), 3.59 (95% CI, 1.83-7.03; $P = 0.0002$), and 3.11 (95% CI, 1.47-6.58; $P = 0.003$), respectively.

Similarly, Peschaud *et al*[53] evaluated the prognostic value of LNRs in rectal cancer. They investigated the relationship between OS, DFS, and LNR in 307 rectal cancer patients. Of the 307 patients, 178 (57.9%) were N0, 67 (21.8%) were N1, and 62 (20.3%) were N2. The mean number of LNs examined was 22. In the multivariate analysis, LNR, and not the presence or absence of metastatic LNs, was found to be a significant prognostic factor for both OS and DFS [HR, 1.019 and 1.016 (95% CI, 1.009-1.029 and 1.008-1.025); $P = 0.0003$ and 0.0002, respectively]. Even in patients with fewer than 12 LNs examined, multivariate analysis confirmed that LNR was an independent prognostic factor for OS and DFS (HR, 1.046 and 1.028; $P = 0.0058$ and 0.0338, respectively).

Interestingly, Derwinger *et al*[55] investigated whether LNR was a prognostic factor in stage IV CRC patients. It is fairly obvious that stage IV CRC is a heterogeneous group with respect to survival prognosis. LNR groups were formed by dividing the patients into 3 equally sized groups: LNR = 0-0.15, LNR = 0.16-0.65, and LNR = 0.66-1. In a univariate analysis, LNR was found to be a significant marker for survival prognosis ($P < 0.0049$). However, the node stage (N1-N2) had a borderline significance ($P < 0.06$). In a Cox multivariate analysis, the performance status and eligibility for chemotherapy were the most significant markers [HR, 2.2 (95% CI, 1.1-4.3), $P < 0.001$] along with the differentiation grade [HR, 2.0 (95% CI, 1.1-2.8), $P < 0.05$]. Concerning LNs, the LNR was significant as a marker [HR, 2.1 (95% CI, 1.3-3.6), $P < 0.05$], while the N stage was not significant.

In 2009, numerous studies on LNRs in CRC patients were published[28,34,57-61]. Vather *et al*[57] reported the significance of LN evaluation in 4309 stage II and stage III colon cancer patients. In stage II and stage III colon cancer patients, the mean numbers of LNs examined were 13.7 and 13.8, respectively. In their study, increased rates of nodal examination were found to be associated with significantly lower 5-year mortality rates for stage II and stage III colon cancer patients, but this survival advantage appeared to be minimal after the 16-node mark. In 2364 stage III colon cancer patients, the 5-year mortality rate showed a clear and steady increase as the LNR increased, with the rate doubling from around 40%-45% in the lowest LNR group to 80%-90% in the higher LNR group. The LNR had a better prognostic discriminative value than the absolute number of positive nodes examined. The LNR has been validated as a powerful predictor of survival in stage III cancer patients.

Chin *et al*[34] determined the relationship between LNR and survival in 624 stage III colon cancer patients. The mean LNR was 0.2045. It was possible to harvest an adequate number of LNs (LN $\geq$ 12) in 490 of the 624 patients (78.5%). The rate of adequate lymphadenectomy was significantly lower in patients with cancer of the descending colon and sigmoid colon than in those with cancer involving all the other areas ($P < 0.001$). These 490 patients were stratified into LNR groups: 1 (LNR $\leq$ 0.4), 2 (0.4 < LNR $\leq$ 0.7), and 3 (0.7 < LNR). Cox proportional hazards regression analysis revealed that the number of positive LNs was not a significant factor [HR, 1.157 (95% CI, 0.811-1.650), $P = 0.421$] when LNR was taken into consideration. They concluded that LNR is a more precise predictor of 5-year DFS than the number of positive LNs in patients with stage III colon cancer [LNR1 *vs* LNR2: HR, 2.298 (95% CI, 1.384-3.815), $P = 0.001$; LNR1 vs. LNR3: HR, 7.407 (95% CI, 3.153-17.397), $P < 0.001$].

Recently, Vaccaro *et al*[61] reported the prognostic value of LNR in stage III colon cancer patients who were treated by colorectal surgeons. The median LNR was 0.11. In all, 362 stage III colon cancer patients were stratified into LNR groups: LNR1 (LNR < 0.25) and LNR2 (LNR $\geq$ 0.25). The 5-year DFS, CSS, and OS for the LNR1 group were 68.3%, 74.5%, and 64.9%, respectively, and were 31.5%, 40.1%, and 38.3% for the LNR2 group, respectively ($P = 0.001$ for each variable). Univariate analysis showed that both LNR and N stage were associated with significantly different HRs for DFS [HR, 2.8 and 2.3 (95% CI, 1.9-4.1 and 1.6-3.4), $P < 0.001$, respectively], CSS [HR, 3.1 and 2.3 (95% CI, 2.1-4.7 and 1.6-3.4), $P < 0.001$, respectively], and OS [HR, 2.2 and 2.0 (95% CI, 1.6-3.2 and 1.4-2.9), $P < 0.0001$ and 0.001, respectively]. In a multivariate analysis, LNR was found to be an independent prognostic factor for DFS [HR, 2.6 (95% CI, 1.5-4.8), $P = 0.001$], CSS [HR, 3.8 (95% CI, 1.9-7.4), $P < 0.001$], and OS [HR, 2.3 (95% CI, 1.3-4.1), $P = 0.005$]. However, N stage was not an independent prognostic factor for DFS ($P = 0.41$), CSS ($P = 0.92$), and OS ($P = 0.58$). In addition, the number of harvested LNs was not a prognostic factor for DFS ($P = 0.39$ and 0.72, respectively), CSS ($P = 0.33$ and 0.41, respectively), and OS ($P = 0.23$ and 0.66, respectively) by univariate and multivariate analyses.

In data obtained in our hospital (unpublished data), we investigated the number of LNs retrieved and the effect of N stage (TNM classification versus Japanese classification) on the 5-year OS in 301 stage III (TNM classification) CRC patients diagnosed between 1985 and 2000. In our hospital, LN identification was performed according to the Japanese system. Briefly, the mesentery of the excised specimen was dissected away from the bowel and LN identification was performed immediately postoperatively by the surgeon before fixation. In all, 157 colon and 144 rectal cancers were documented. The mean numbers of retrieved and metastatic LNs were 22.9 and 3.2, respectively. Adequate LN evaluation (i.e. examination of at least 12 LNs) was performed in 226 of the 301 (75.1%) patients. As per the TNM classification, the group of patients with N1 ($n = 220$) and N2 ($n = 81$) had a 5-year OS

of 84.9% and 50.1%, respectively, while according to the Japanese classification, the group of patients with N1 (n = 212), N2 (n = 65), and N3 (n = 24) displayed a 5-year OS of 83.0%, 64.0%, and 40.0%, respectively. Hence, the prognostic separation using the Japanese classification system was 43.0% and that using the TNM classification system was 34.8%. In colon cancer, the mean numbers of retrieved and metastatic LNs were 21.7 and 2.9, respectively. Adequate LN evaluation was performed in 117 of the 157 (74.5%) patients. The groups of patients with N1 (n = 121) and N2 (n = 36) (TNM classification) had a 5-year OS of 91.0% and 55.0%, respectively, while that with N1 (n = 116), N2 (n = 33), and N3 (n = 8) (Japanese classification) had a 5-year OS of 90.7%, 62.4%, and 31.3%, respectively. Hence, the prognostic separation using the Japanese classification system was 59.4% and that using the TNM classification system was 36.0%. In rectal cancer, the mean numbers of retrieved and metastatic LNs were 24.3 and 3.5, respectively. Adequate LN evaluation was performed in 109 of the 144 (75.7%) patients. The groups of patients with N1 (n = 99) and N2 (n = 45) (TNM classification) had a 5-year OS of 77.6% and 49.1%, respectively, while that with N1 (n = 96), N2 (n = 32), and N3 (n = 16) (Japanese classification) displayed a 5-year OS of 75.7%, 65.7%, and 35.5%, respectively. Hence, the prognostic separation using the Japanese classification system was 40.2% and that using the TNM classification system was 28.5%. Therefore, in our analysis, N stage using the Japanese classification system was found to be remarkably superior to the TNM classification system for the stratification of prognosis.

CONCLUSION

In the literature on the number of LNs retrieved, as shown in Table 1, 12 of 17 articles assessed 12 or more nodes[26,28,34,50-53,57-61]. In many studies that were reviewed in this editorial, more than 12 LNs were investigated. However, a population-based analysis revealed that only 37% of patients with CRC received adequate LN evaluation (i.e. at least 12 LNs examined)[29]. To correct this, it may be useful for the method of LN identification in the mesenterium be changed to the Japanese system rather than the Western system after adequate lymphadenectomy.

Some reports showed the advantage of using the LNR compared to the absolute number of LNs and/or LN status (N stage or number of positive LNs). With respect to the retrieval number of LNs in stage III CRC, when increasing numbers of LNs are examined, an associated improvement in OS and/or DFS was observed[22,26-28]. However, in some reports, an associated improvement in OS and/or DFS was not observed[50,52,56,59-61]. When taking the LNR into consideration, the retrieval number of LNs was not always found to be a prognostic factor. In contrast, for the LN status (N stage or number of positive LNs), as the LN status decreased, there was an associated improvement in the OS and/or DFS[22,27,48,52,56,59,60]. However, in some reports, such an improvement was not observed[51,61]. When the LNR was taken into consideration, LN status was not always found to be a prognostic factor. The clinical significance of LN status as a prognostic factor is not necessarily absolute.

However, these studies vary widely in sample size and tumor background. It is not known whether a systematic examination of LNRs across all patients would yield consistent results. Although the body of literature regarding LNRs is growing, many studies have been performed using diverse patient groups. When LNR is taken into consideration, the cut-off points have not necessarily been discussed adequately or validated in alternative data sets. We believe that systematic LNR analyses from multi-institutional randomized patient data with validation in similar independent data sets are required to clearly demonstrate the importance of LNRs. The cut-off points for LNRs in grouping patients or for recommending adjuvant therapy have yet to be established. It is essential to consider the staging system to include accurate prognostic variables such as LNR. Cut-off points for LNRs were proposed in numerous studies, but the optimal threshold for LNRs has not received consensus. It is still unclear whether LNR has more prognostic validity than N stage or the number of positive LNs. For all these reasons, the potential advantages of LNRs in staging systems should be investigated in large prospective data sets.

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Challenges in Staging Systems for Colorectal Cancer: Clinical Significance of Metastatic Lymph Node Number in Colorectal Cancer and Mesorectal Extension in Rectal Cancer

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Key Words

Staging system for colorectal cancer • Number of metastatic lymph nodes • Mesorectal extension

Abstract

In many countries, treatment for cancer is performed based on staging systems in which the degree of cancer development is defined objectively. A common staging system is thus needed to compare outcomes. The staging system for colorectal cancer in Japan has been made to enhance consistency with the TNM classification, and the categorization of metastatic lymph nodes and depth of invasion have been revised in recent years. Although these are important factors that determine disease stage, relationships between each factor and recurrence have shown differing prognoses. In our retrospective study, the prognosis of a group with only one metastatic lymph node was significantly better compared to a group with ≥2 metastatic lymph nodes. In addition, rectal cancer with mesorectal extension >5 mm showed low relapse-free survival rates and high recurrence rates. The validity of staging systems should thus be inspected from various perspectives.

Introduction

Predicting prognosis and determining guidelines for therapeutic strategies is important in patients with carcinoma. A staging system that can objectively express the degree of carcinoma development is thus necessary. Around the world, various well-known staging systems are used to reflect prognosis for colorectal cancer such as Dukes classification [1], the Astler Coller classification [2] and TNM classification [3]. Moreover, original staging systems are used in other countries, such as the UK and Australia.

In Japan, original clinical studies on colorectal cancer have been repeated and general rules for clinical and pathological studies of cancer of the colon, rectum and anus have been modified and applied on the basis of those results [4]. The important prognostic factors for colorectal cancer are depth of invasion and regional lymph node metastasis, and these factors are used to determine disease stage [1, 5–7]. However, definitions of the degree of metastasis to lymph nodes and depth of invasion vary slightly between each staging system. A standard staging system allowing the comparison of procedure is necessary if the globalization of cancer therapy is to advance.

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From this perspective, in the 7th Japanese edition of the general rules for clinical and pathological studies on cancer of the colon, rectum and anus, considerable changes have been made to enhance consistency with both the TNM classification and Japanese classifications of other gastrointestinal cancers [8]. Classification of lymph nodes in our country has been grouped in part in a principal bronchus artery such as the inferior mesenteric artery. The pericolic nodes along the marginal arteries were classified as N1, the lymph nodes at the pedicle of the principal vessel chosen were classified as N3, and the lymph nodes between N1 and N2 were classified as N2.

In terms of the grading of lymph node metastasis, classification by both grouping which was mentioned above and the number of regional lymph node metastases was considered from the classification by grouping alone [8]. However, conventional classification by grouping appears to reflect the prognosis in some groups. Furthermore, in the TNM classification, ≤3 metastases to lymph nodes are provided as N1 and ≥4 as N2. However, doubt remains about the basis and validity of this cut-off.

Regarding depth of invasion, some problems remain in the diagnosis of extramural infiltration in parts without serosa. In the Japanese Classification of Colorectal Carcinoma (JCCRC), tumor invasion infiltrating through the muscularis propria in the part without serosa is classified as slight invasion (A1) or deep invasion (A2). However, this definition is vague and no prognostic difference between these categories has been shown. Given these facts, the classification of tumor invasion has been revised so that tumor invasion through the muscularis propria (T3 in the TNM classification) is represented by 'A' in Japan [8]. The degree of invasion has been suggested to correlate with prognosis, so there seems to be room for examination of this point.

The present study investigated relationships between the degree of lymph nodes metastasis, extent of tumor invasion and prognosis. We then reviewed an outline of the significance of these relationships.

Materials and Methods

Metastatic Lymph Node (MLN) Patients

From 1975 to 2000, a total of 462 consecutive patients with Dukes C colon cancer treated by curative resection were collected from the colorectal cancer database of Kurume University, Fukuoka, Japan. The median age of these patients was 62 years, and 290 patients were male (62.7%). Colon lesions were present in 215 patients, with rectal lesions in 247. The median number of retrieved lymph nodes was 29 (range 28–50, average 32.2 ± 18.1), and median duration of follow-up was 68 months (range 24–186, average 60.5 ± 22.3). These cases were classified by the number of MLNs and the survival rate of each group was determined. Then a new appropriate classification was considered from the number of cases and survival rate. In a new classification, a survival rate was reviewed again and prognostic-related factors were inferred statistically.

Mesorectal Extension (ME) Patients

From 1982 to 1990, a total of 220 consecutive patients with rectal cancer (Dukes B, n = 114; Dukes C, n = 106) treated by curative resection were collected from the colorectal cancer database of Kurume University, Fukuoka, Japan. Patients who received preoperative radiotherapy were excluded. Overall median follow-up was 75 months (range 6–198). The endpoint for survival was the time at recurrence of rectal cancer. Relationships between recurrence and distance of ME and other clinicopathological factors were analyzed statistically.

Measurement of ME

Measurement of ME was performed as follows. When the layer of muscularis propria was completely torn, the distance perpendicular to the straight line between both inferior margins of the torn muscularis was measured (fig. 1a). When the continuity of the muscularis propria layer was unclear, the judgment of the rift was assumed of the degree of tearing and the distance from the muscularis propria to the deepest part of the carcinoma was measured (fig. 1b).

Statistical Methods

Analysis of variance or a t test were used to analyze continuous variables. A χ^2 approval was used for categorical variables. Five-year survival rates and prognostic factors were estimated using the Kaplan-Meier survival method and Cox proportional hazard regression model, respectively. A multivariate statistical study using Cox proportional hazard modeling was applied to identify independent variables influencing survival. Values of $p < 0.05$ were considered statistically significant. Statistical analysis was performed using StatView 5.0 software (SAS Institute Inc., Cary, N.C., USA).

Results

MLN Analysis

Survival rates were compared for groups classified by the number of MLNs. The 5-year survival rate (number of cases, median number of retrieved lymph nodes) for each group were as follows, respectively: 1 MLN, 80.2% (163 cases, 28 nodes); 2 MLNs, 68.1% (83, 29); 3 MLNs, 69.2% (64, 31); 4 MLNs, 71.7% (49, 34); 5 MLNs, 68.1% (26, 33); 6 MLNs, 68.6% (19, 43); 7 MLNs, 59.3% (11, 36); 8 MLNs, 49.7% (12, 41); 9 MLNs, 32.7% (10, 48), and ≥10 MLNs, 29.9% (25, 50). Thus the 5-year survival rate for the group with 1 MLN was significantly better than the other groups. And the group with ≥7 MLNs showed a

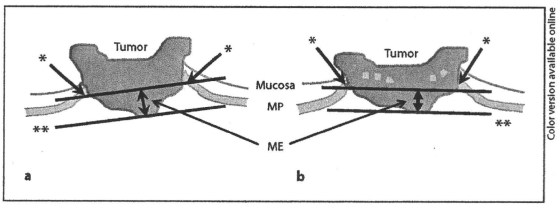

Fig. 1. Method of measurement of mesorectal extension (ME). **a** Muscularis propria (MP) completely and clearly torn. **b** Unclear status of MP. * MP bottom line between both inferior margins. ** Tumor bottom line.

significantly lower survival than groups with ≤6 MLNs. Based on the above-mentioned results, the survival curve of each group (data not shown), survival rate, patient number and current classification were considered and integrated and reorganized into five groups.

The new classification used 1 MLN for group A (163 cases), 2 MLNs for group B (83 cases), 3 MLNs for group C (64 cases), 4–6 MLNs for group D (94 cases), and >6 MLNs for group E (58 cases). The 5-year survival rate and relapse-free survival rate for each group were: A, 80.2 and 75.5%; B, 67.0 and 62.0%; C, 66.3 and 61.9%; D, 66.8 and 61.9%, and E, 39.6 and 39.6%, respectively. The survival curves of groups B–D were similar (fig. 2). This classification such as group A, groups B–D and group E was thus more capable than conventional categories such as groups A–C and groups D–E. In brief, MLN categories seemed the most adequate when the number of metastases was classified as 1, 2–6, or ≥7. Factors influencing prognosis were statistically extracted from clinicopathological factors of every group. Furthermore, correlative prognostic factors included in the new classification of MLN degree were estimated with uni- and multivariable analyses (table 1). As for independent prognostic factors, preoperative carcinoembryonic antigen level, degree of vessel invasion, and MLN number were extracted.

ME Analysis

Median ME was 3.8 mm (range 0.2–30, average 4.9 ± 4.3). The cut-off value of ME was determined as follows. Measured ME values were divided every 1 mm and classified into two groups (e.g., <1 vs. ≥1 mm, <2 vs. ≥2 mm, <3 vs. ≥3 mm, <4 vs. ≥4 mm, ...). These groups were compared with disease-free survival respectively and each p value was calculated. The cut-off value was fixed for the ME value associated with the lowest p value by comparison between the above two groups, and was considered as a factor influencing recurrence.

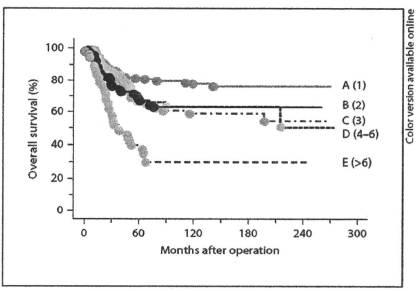

Fig. 2. Survival curve according to the number of metastatic nodes.

When the cut-off value for ME was fixed at 5 mm for rectal cancer, the p value by comparison of relapse-free survival between groups (<5 vs. ≥5 mm) was lowest. Clinicopathological factors related to recurrence of rectal cancer were location (upper/lower), operative procedure (anal preservation/no preservation), tumor gross type (localized type/invasive type), depth of invasion (a1/a2), histologic type (well/others), lymphatic invasion (negative/positive), MLNs (negative/positive) and pelvic lymph node metastasis (negative/positive), according to univariate analysis. Adding ME (<5/≥5 mm) to these factors, multivariate analysis was performed, sphincter-preserving operation (yes/no), depth of invasion (a1/a2), lymphatic invasion (negative/positive), MLNs (negative/positive), pelvic lymph node metastasis (negative/positive) and actual measurement ME (<5/≥5 mm) were extracted as independent risk factors for recurrence (table 2).