TABLE 2 continued

Variable	Univariate analysis P-value	Multivariate analysis		
		P value	Hazard ratio	95% CI
Stage	<0.0001	NS		
Adjuvant chemotherapy	<0.0001	NS		
Radiotherapy	<0.0001	0.0266		
Yes			1.79	1.07–3.04
No			1.00	
Lateral lymph node dissection	<0.0001	NS		

[a] The degree of invasion was divided into 4 grades according to the Japanese criteria[18]

ly0 no invasion, *ly1* minimal invasion, *ly2* moderate invasion, *ly3* marked invasion, *LN* lymph node, *LNR* lymph node ratio, *CI* confidence interval, *NS* not significant

TABLE 3 Significance of prognostic factors by stage and location

Variable	AUC		
	Stage 1	Stage II	Stage III
Colon			
Depth of invasion	0.548	0.559	0.606
Total number of LNs examined	0.560	0.654	0.517
Number of metastatic LNs	–	–	0.624
Lymphatic invasion	0.604	0.583	0.592
Adjuvant chemotherapy	0.505	0.507	0.505
Rectum			
Depth of invasion	0.503	0.531	0.615
Total number of LNs examined	0.513	0.567	0.505
Number of metastatic LNs	–	–	0.665
Adjuvant chemotherapy	0.527	0.523	0.518
Radiotherapy	0.507	0.534	0.513

LN lymph node, *AUC* area under the receiver operating characteristic curve

nodes or the proportion of patients having at least 12 nodes counted. Results show that average annual hospital case volume more significantly correlated with 12-node measure compliance ($r^2 = 0.351$; $P = 0.009$) rather than the average number of retrieved nodes ($r^2 = 0.164$; $P = 0.096$). The top lymph node-counting tertile of hospitals collected at least 12 nodes in 81.8% of cases, whereas the 12-node measure was compliant with 71.5% of patients in the middle group of hospitals and 50% of patients in the lowest group of hospitals.

DISCUSSION

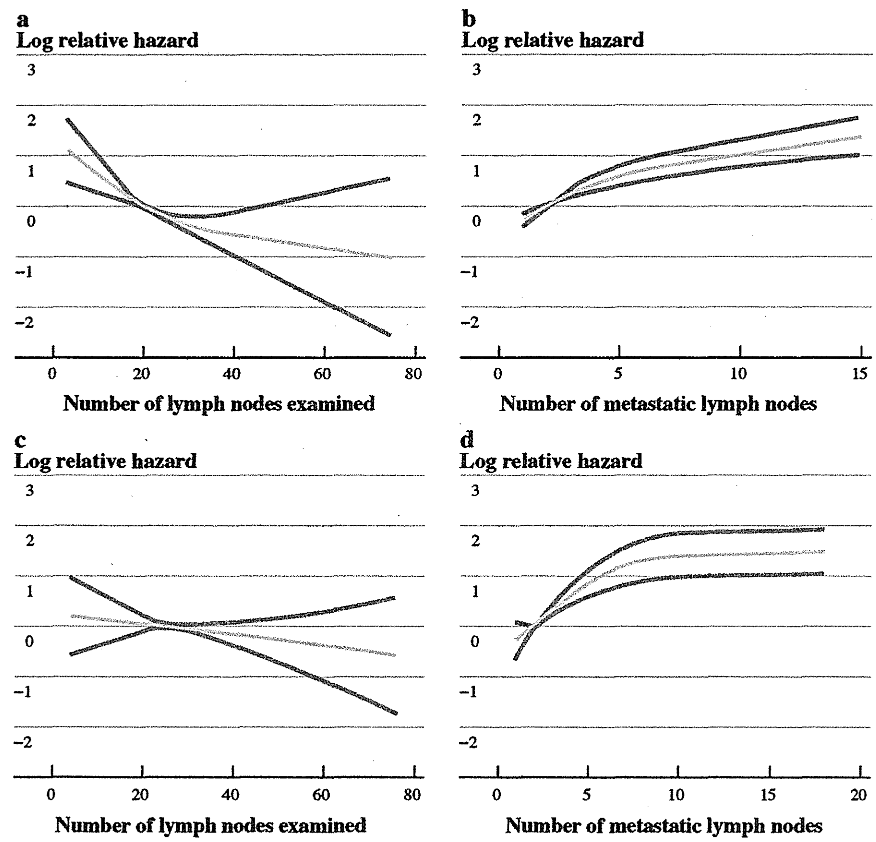
Lymph node status is a strong predictor of colorectal cancer survival and frequently dictates treatment decisions. Our study confirms that the number of lymph nodes identified in resected colorectal cancer specimens can be influenced by multiple factors.[24] In this study, female sex, younger age (<60 years), rectal and right-sided colon tumors, larger tumor diameter, and higher T or TNM stage were associated with more retrieved nodes. Several studies have shown that tumor location is significantly associated with the number of lymph nodes in resection specimens. In our series, total mesorectal excision with extended lateral pelvic lymphadenecotmy was performed for lower rectal cancer with T2 or higher stages,[25,26] and this increased the number of nodes retrieved from rectal cancers. In this study, hospital factors also influenced lymph node retrieval, thus suggesting that underlying surgical and pathologic practice patterns and patient volumes may play an important role in adequate lymph node evaluation.

Studies of survival in various stages of colorectal cancer have generally concluded that resection of too few nodes is a poor prognostic indicator. This study confirms this conclusion and extends it across stage II and III disease. DSS is significantly greater in stage II patients when more lymph nodes are examined for both colon and rectal cancer. Increasing lymph node yields were associated with a decreased risk of death without reaching a hazard plateau, leading us to recommend that as many nodes as possible should be analyzed. DSS was also predicted by the number of positive nodes identified in stage III patients, which was strongly related with the log hazard of death, especially in rectal cancer. Our study clearly showed that the number of lymph nodes examined and the number of positive nodes are both important in determining prognosis for colorectal cancer.

It may be argued that the number of nodes examined is of greater importance in node-negative disease than in node-positive cases. If a patient is node negative after only a few nodes have been examined, the likelihood of understaging is significant. Scott and Grace[11] estimated that failure to identify at least 13 lymph nodes led to a false-negative rate of 10%. Joseph et al.[10] developed a mathematical model to calculate the probability of a missed nodal metastasis according to the number of nodes examined. On the basis of these and other studies, various guidelines suggest minimum counts of 8–40 nodes, including a recommendation from the College of American Pathologists for an arbitrary 12-node minimum.[10,11,13,27–30] However, these recommendations are based on observational studies, many of which do not adjust for potentially confounding variables. In addition, some of the studies are from single institutions,[10,13] and this may reflect underlying institutional surgical and pathologic practice and may not be generalizable to the population at large.

Our approach differs markedly from the aforementioned studies. The Japanese general rules[18] divide regional lymph node spread in colorectal cancer into three levels: N3,

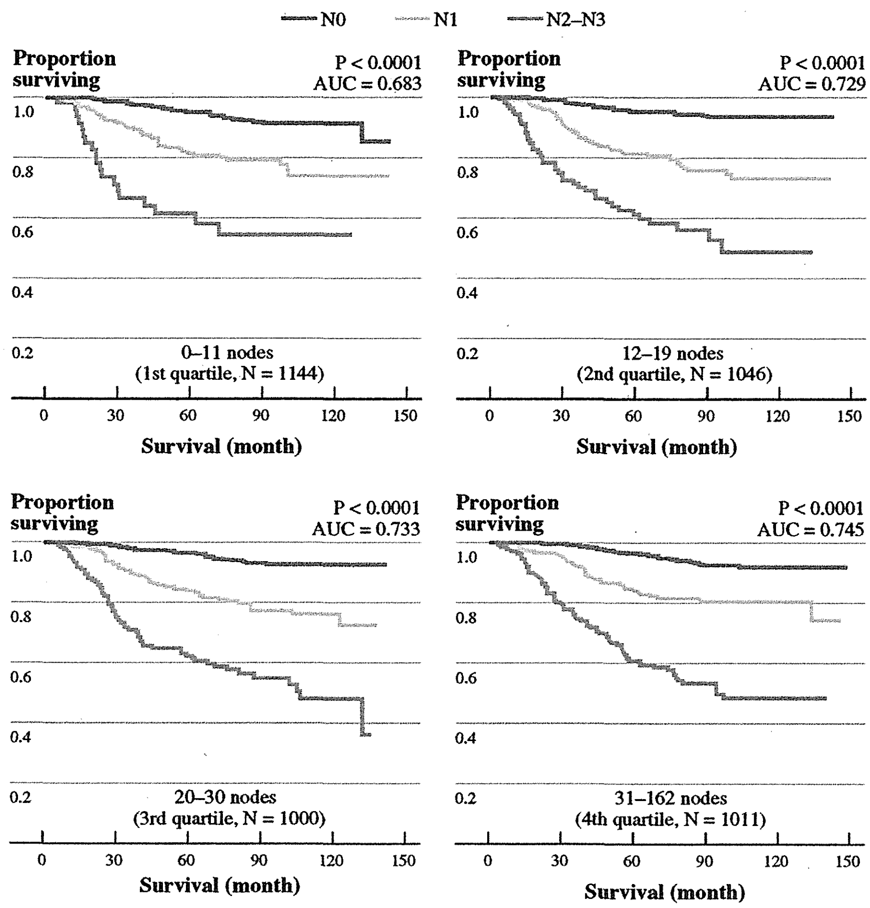
FIG. 1 Plots showing the relationship of predictors with hazard of death. *Blue lines* represent 95% confidence intervals. **a** Stage II colon cancer, **b** stage III colon cancer, **c** stage II rectal cancer, **d** stage III rectal cancer



metastasis in the main or lateral pelvic lymph nodes; N2, metastasis in 4 or more pericolic/perirectal or intermediate lymph nodes; and N1, metastasis in 1–3 pericolic/perirectal or intermediate lymph nodes. In addition, the Japanese Research Society for Cancer of the Colon and Rectum[18] advocates recording the lymph node groups removed and, since the 1970s, has considered a complete dissection of all regional nodes only if the specimen contained the central (D3) nodes. They strictly follow guiding principles for colorectal cancer surgery, i.e., en-bloc removal of the cancer with adequate proximal and distal margins, and inclusion of the regional mesenteric lymphatics following anatomic landmarks. Therefore, to the Japanese surgeon who is also an investigator, adequate lymphadenecotmy is synonymous with adequate mesenteric excision. In this study, the survival of patients was stratified by N-stage throughout all strata of lymph nodes examined, which is compatible to the notion of regional lymph node spread burden. However, retrieval of fewer than 12 nodes with a cutoff based on quartiles was an unfavorable factor to discriminate between patients who survive and those who do not, because the area under the receiver operating characteristic curve for the stratum of 0–11 nodes was the lowest value of 0.683 among the strata of retrieved nodes. This suggests an inferior predictive capacity within individual patients with fewer than 12 retrieved lymph nodes. Generally, a model that performs with receiver operating characteristic measures of 0.7–0.8 is considered good, whereas values of 0.81–0.90 are considered excellent.[31] There was also a steady increase in the index of discrimination with an increasing number of lymph nodes examined. Hence, it is conceivable that some patients with adequately staged N2 disease have undetected nodes indicative of N3 with fewer resected lymph nodes. These findings support the importance of sufficient node examination. The potential risk of understaging can be reduced by retrieval of at least 12 nodes during radical resection and achieving wider mesenteric excision with central vascular ligation.[32]

The true effect of lymphadenectomy remains debated,[33] as does the minimum number of nodes necessary for an adequate resection. We found that survival improved with increasing node counts at the individual patient level after adjustment for confounders. This is in agreement with previous studies that reported that an increasing number of retrieved nodes corresponded with increased survival.[3,34] Such a relationship may be due to stage migration[35] or due to a decrease in local recurrence and distant metastasis with

FIG. 2 Disease-specific survival by extent of nodal examination and Japanese N stage



resection of affected lymph nodes. We presented a method designed to circumvent the stage-migration effect that can give direct information on hospital lymph node counts and T-stage. When hospital lymph node count volume was categorized roughly into tertiles based on the total number of lymph nodes examined by individual hospitals, patients treated at hospitals with higher average node counts experienced better survival than patients treated at hospitals with lower average node counts for each T-stage. In particular, the group of hospitals with the highest lymph node counts in T4 disease had a more than 8% higher DSS at 5 years than the middle and lowest groups. These findings suggest that a more extensive nodal dissection may result in more optimal margins of surgical resection, which improves local recurrence rates and survival by diminishing the possibility of residual micrometastatic disease acting as a source for distant metastasis. Previous studies have shown that colon cancer patients treated at high-volume specialized cancer centers have better long-term outcomes (e.g., recurrence and survival) than those treated at low-volume community hospitals.[36,37] In this study, hospital case volume was mildly correlated with the identification of 12 or more lymph nodes. Furthermore, there were many differences in the 12-node measure between hospital lymph node count tertiles. It is possible that lymph node recovery or detection varies according to hospital volume, thus addressing the implications of the 12-lymph node quality indicator for colorectal resections at individual hospitals.

Our study demonstrates evidence of improved staging and oncologic outcomes when more lymph nodes are identified. These observations do not address the issue of whether the improved outcomes are from improved staging, improved clearance of micrometastatic disease, or perhaps a combination of these and other factors. However, we have shown that the relationship between number of nodes and staging is not simple. There were three major influences on the total number of nodes harvested: the hospital, with regard to quality of surgical and pathologic care and case volume; patient characteristics, with regard to age and sex; and tumor properties, with regard to tumor site, size, depth of invasion, and stage. The number of lymph nodes examined reflects an interaction among these factors. The retrieval of a small number of lymph

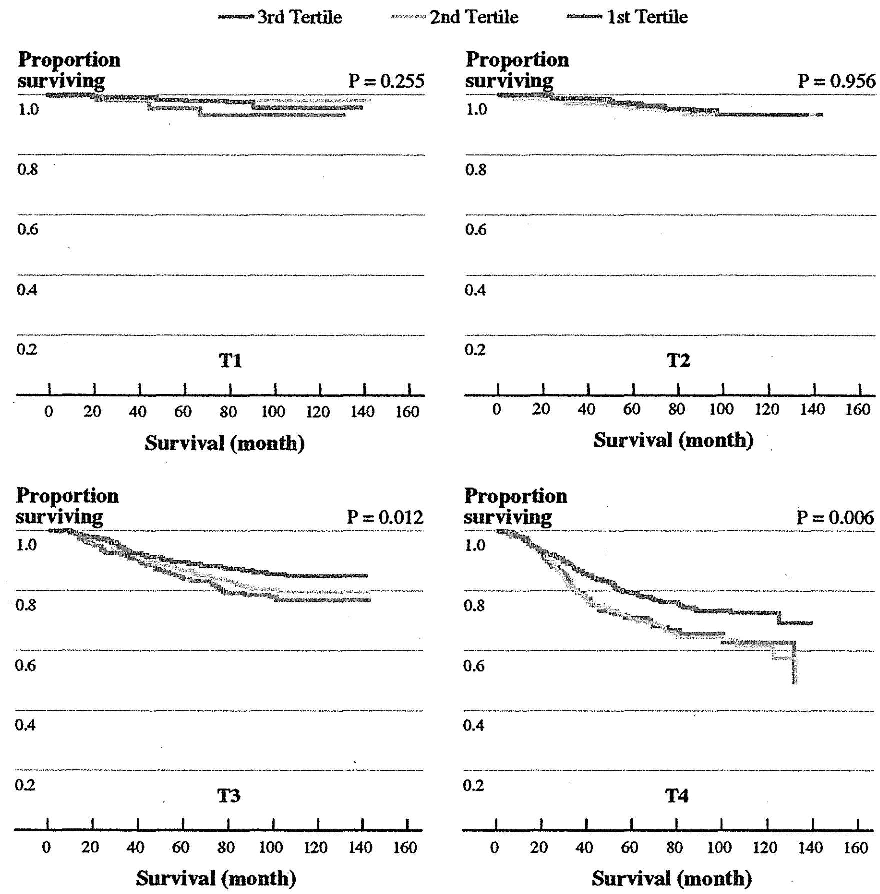


FIG. 3 Disease-specific survival by T stage and hospital lymph node count tertile

nodes may be an indicator of poor surgical or pathologic quality. The controllable factors for surgery and pathologic examination include exertion of maximum effort to provide every patient with an optimal chance for appropriate treatment and cure. At least a 12-node threshold is supported as a measure to improve a discriminatory capacity in prognosis and as a quality-control parameter of hospital performance in colorectal cancer surgery. Efforts to retrieve as many nodes as possible may further decrease adverse oncologic outcomes.

APPENDIX

The authors completed this study in collaboration with the following: K. Hirata (Sapproro Medical University), A. Murata (Hirosaki University), K. Hatakeyama (Niigata University), K. Hase (National Defense Medical College), K. Kotake (Tochighi Cancer Center), T. Masaki (Kyorin University), S. Kameoka (Tokyo Women's Medical University), H. Hasegawa (Keio University), K. Takahashi (Tokyo Metropolitan Cancer and Infectious disease Center), Y. Saito (International Medical Center of Japan), K. Sugihara (Tokyo Medical and Dental University), T. Watanabe (Teikyo University), K. Maeda (Fujita Health University), T. Hirai (Aichi Cancer Center), Y. Sakai (Kyoto University), M. Ooue (Osaka Medical Center for Cancer and Cardiovascular Diseases), N. Tomita (Hyogo College of Medicine), and K. Shirouzu (Kurume University).

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ORIGINAL ARTICLE

Laparoscopic resection for sigmoid and rectosigmoid colon cancer performed by trainees: impact on short-term outcomes and selection of suitable patients

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Abstract

Purpose This study aimed (1) to evaluate the impact of clinical factors, particularly operation by trainees, on the short-term outcomes of laparoscopic resection for sigmoid and rectosigmoid cancer, and (2) to determine patients suitable for operation by trainees.

Methods From a prospectively maintained single-institution database, we identified 133 patients who underwent laparoscopic resection for sigmoid or rectosigmoid cancer between 2007 and 2010. Gender, age, body mass index (BMI), previous abdominal surgery, tumor location, tumor size, tumor stage, extent of lymph node dissection, and primary surgeon were evaluated using univariate and multivariate analyses to determine the predictive significance of these variables on surgical outcomes including operative time, blood loss, complication, postoperative stay, and retrieved lymph nodes.

Results Multivariate analysis showed that location of the tumor in the rectosigmoid ($p<0.001$), higher BMI ($p<0.001$), operation by trainees ($p<0.001$), male gender ($p=0.002$), and greater tumor depth ($p=0.011$) were independently predictive of longer operative time. Larger tumor size ($p=0.025$) and higher BMI ($p=0.040$) were independently predictive of greater blood loss. Larger tumor size was also related to longer postoperative stay ($p=0.001$) and a greater number of retrieved lymph nodes ($p=0.001$).

Conclusions This study identified operation by trainees as an independent risk factor for longer operative time but with no negative impact on any of the other outcomes. Female patients with a low BMI, sigmoid cancer, shallow tumor depth, and/or small tumor are suitable for operation by trainees.

Keywords Laparoscopic surgery · Colorectal resection · Sigmoid cancer · Laparoscopic training · Patient selection · Trainees

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Introduction

Laparoscopic approaches are accepted for colorectal cancer surgery. Several randomized clinical trials of laparoscopic versus open colectomy for colorectal cancer suggest equivalent long-term outcomes with both techniques [1–7]. It is currently inevitable that laparoscopic colorectal procedures are included in general surgery training programs due to their increasing popularity. However, a suitable training program has not yet been developed for the clinical setting [8–11]. Laparoscopic training for surgical residents often begins with basic laparoscopic colorectal procedures such as laparoscopic sigmoid and rectosigmoid resection. During the training period, careful patient selection is essential for maintaining the quality and safety of the procedure performed by novice surgeons. This study aimed (1) to evaluate the impact of clinical factors, particularly operation by trainees, on the short-term outcomes of laparoscopic resection for sigmoid and rectosigmoid cancer, and (2) to select suitable patients for operation by trainees.

Methods

Patients

From a prospectively maintained single-institution database, we identified 156 consecutive patients who underwent laparoscopic resection for sigmoid or rectosigmoid cancer between 2007 and 2010. The indications for laparoscopic surgery were colon cancer tumors without forming a bulky mass, massive lymph node involvement, or invasion of the adjacent organs, as determined by using computed tomography during preoperative examinations. An additional indication was evidence of metastatic disease that could not be curatively resected using open surgery. The surgeries were performed by an experienced, board-certificated, expert surgeon (T.Y.) or by six trainees; of these trainees, four had no prior experience in open or any laparoscopic surgeries and two had experience (2 and 12 years) in open and only basic laparoscopic surgeries. In the first step, trainees with no experience were required to act as endoscopists for about 20 laparoscopic colorectal procedures and encouraged to view a collection of video recordings of laparoscopic colectomy in order to learn the essentials of the standardized techniques used in these operations. They experienced other basic laparoscopic procedures (e.g., cholecystectomy, stoma creation, omental patch repair for gastroduodenal perforation) in the same term. However, 4–6 months later, they proceeded to the next step, in which they started to act as primary surgeons during oncologic laparoscopic colorectal procedures such as laparoscopic sigmoid or ileocecal resection under the supervision of the expert surgeon, thereby acquiring basic laparoscopic skills (prior experience in open colon surgery was not required). In the present study, we excluded 23 patients who underwent Hartmann's procedure or simultaneous resection of other organs. The remaining 133 patients were evaluated. Data on gender, age, body mass index (BMI), previous abdominal surgery, tumor location, tumor size, tumor depth, tumor stage, extent of lymph node dissection, primary surgeon, operative time, blood loss, conversion to open surgery, pathology, 30-day morbidity, mortality, and postoperative stay were collected prospectively. Tumors were staged according to the sixth tumor–node–metastasis classification of the International Union Against Cancer on the basis of the histological findings of the surgical specimens. The protocol was approved by the local ethics committee, and informed consent was obtained from all participating patients.

Surgical procedures

Patients were placed in the Lloyd–Davis position with the head and right side of the bed lowered. First, a 12-mm camera port was inserted below the umbilicus with the open method. After creation of a pneumoperitoneum, four working ports were inserted: 5-mm ports in the right and left upper abdominal quadrants, and 12-mm ports in the right and left lower abdominal quadrants. The mesocolon was mobilized using the mediolateral approach, and no splenic flexure mobilization was needed. In accordance with the oncologic surgical principles recommended by the Japanese Society for Cancer of the Colon and Rectum [12, 13], a D3 lymph node dissection, including the pericolic nodes (local nodes), mesocolic nodes (intermediate nodes), and nodes at the origin of the inferior mesenteric artery (IMA) (main nodes), was performed with division of the IMA at its origin, except in the case of elderly patients or tumors confined to the submucosa, in which case a D2 lymph node dissection, which includes only the local and intermediate nodes, with division of the IMA distal to the first branch to the descending colon (the origin of the superior rectal artery [SRA] or sigmoid artery [SA]) was performed. The distal colon or rectum was transected intracorporeally using an Endopath Endo-Cutter or Echelon 60 (Ethicon Endo-Surgery, Cincinnati, OH, USA). Then, the specimen was extracted through the left lower quadrant port or the camera port, which was extended to about 4 cm. Anastomosis was performed intracorporeally by the double-stapling technique or extracorporeally by functional end-to-end anastomosis.

Statistical analysis

All statistical analyses were performed using Statistical Package for Social Sciences™ (SPSS) version 15.0 (SPSS Inc., Chicago, IL, USA), and significance was defined as $p<0.05$. Where appropriate, we used Fisher exact tests, chi-square tests, Student's t tests, Welch's tests, or Pearson product–moment correlation coefficients to investigate the relationships between the patients' clinical characteristics and surgical outcomes. A multivariate analysis was performed using a multiple linear regression model with a stepwise method (significance level to enter=0.05; significance level to stay=0.1) or a multiple logistic regression model.

Results

The number of laparoscopic colorectal cancer resections performed by the expert and novice surgeons between 2007 and 2010 are shown in Table 1. Trainees performed a substantial portion of the laparoscopic resections for tumors in the ascending, sigmoid, and rectosigmoid colon and the cecum (209 [82.3 %] of 254 cases), which was significantly higher than that for tumors in other locations (75 [54.3 %] of 138; $p<0.001$).

The patients and tumor characteristics of the 133 patients included in the study are summarized in Table 2. Gender,

Table 1 The number of laparoscopic resections in each tumor location

Tumor location [*n* (%)]	Performed by expert	Performed by trainees	Total
Cecum	4 (13.3)	26 (86.7)	30
Ascending colon	15 (22.1)	53 (77.9)	68
Transverse colon	11 (27.5)	29 (72.5)	40
Descending colon	11 (42.3)	15 (57.7)	26
Sigmoid/rectosigmoid colon	26 (16.7)	130 (83.3)	156
Upper rectum	18 (48.6)	19 (51.4)	37
Lower rectum/anal canal	23 (65.7)	12 (34.3)	35
Total	108 (27.6)	284 (82.4)	392

mean age, mean BMI, and previous history of abdominal surgery were similar between the groups. Tumor size was significantly larger (5.1 cm versus 3.1 cm; $p<0.001$), and the incidence of T3/T4 tumors was significantly higher (81.8 % versus 49.5 %; $p=0.011$) in the patients operated on by the expert surgeon than in the patients operated on by the trainees. On the contrary, nodal involvement and tumor stage were not different. The incidence of D3 lymph node dissection was significantly higher for the expert surgeon than for the trainees (86.4 % versus 63.1 %; $p=0.046$).

Operative outcomes are summarized in Table 3. Operative time was significantly longer in the patients operated on by the trainees than in those operated on by the expert surgeon (244.2 min versus 214.7 min; $p=0.007$), but blood loss was not significantly different. The incidence of patients with less than 12 retrieved lymph nodes was larger in surgeries performed by the trainees than in surgeries performed by the expert (22.5 % versus 4.5 %), but the difference was not statistically significant ($p=0.074$). The overall morbidity rate was 9 (6.8 %) in 133 patients with a

Table 2 Patient clinical characteristics

	Performed by expert ($n=22$)	Performed by trainees ($n=111$)	*P* value
Gender (male/female) (range)	12 (54.5)/10 (45.5)	66 (59.5)/45 (40.5)	0.669
Age (years) (range)	68.5 (44–85)	67.7 (31–93)	0.766
Body mass index (kg/m^2) (range)	23.1 (18.4–28.0)	22.5 (14.8–28.8)	0.465
Previous abdominal surgery [n (%)]	5 (22.7)	37 (33.3)	0.467
Tumor location (sigmoid/ rectosigmoid) [n (%)]	18 (81.8)/4 (18.2)	79 (71.2)/32 (28.8)	0.445
Tumor size (cm) (range)	5.1 (0–9)	3.1 (0–7)	<0.001
Pathologic T stage [*n* (%)]			(Tis/T1/T2 vs. T3/T4)
Tis	1 (4.5)	9 (8.1)	0.011
T1	3 (13.6)	32 (28.8)	
T2	0 (0)	15 (13.5)	
T3	7 (31.8)	16 (14.4)	
T4	11 (50)	39 (35.1)	
Pathologic N stage [*n* (%)]			(N0/N1 vs. N2)
N0	13 (59.1)	69 (62.2)	0.745
N1	6 (27.3)	27 (24.3)	
N2	3 (13.6)	15 (13.5)	
Tumor stage [*n* (%)]			(0/I/II vs. III/IV)
0	1 (4.5)	8 (7.2)	0.837
I	3 (13.6)	40 (36.0)	
II	9 (40.9)	18 (16.2)	
III	8 (36.4)	35 (31.5)	
IV	1 (4.5)	10 (9.0)	
Lymph node dissection (D3/D2) [*n* (%)]	19 (86.4)/3 (13.6)	70 (63.1)/41 (36.9)	0.046
Anastomosis (DST/FEEA) [*n* (%)]	19 (86.4)/3 (13.6)	96 (86.5)/15 (13.5)	1

All continuous variables are described as mean with range

DST double stapling technique, *FEEA* functional end-to-end anastomosis

Table 3 Surgical outcomes

	Performed by expert (n=22)	Performed by trainees (n=111)	P value
Operative time (min) (range)	214.7 (149–336)	244.2 (150–417)	0.007
Blood loss (ml) (range)	31.6 (0–340)	16.8 (0–590)	0.140
Transfusion	0	0	NA
Intraoperative complication [n (%)]	0	1 (0.9)	1
Tear in the rectal stump	0	1 (0.9)	1
Conversion [n (%)]	0	0	NA
Positive circumferential resection margin	0	0	NA
Number of retrieved lymph nodes <12 [n (%)]	1 (4.5)	25 (22.5)	0.074
Postoperative complication [n (%)]	2 (9.1)	7 (6.3)	1
Anastomotic leakage	0	0	
Wound infection	0	6 (5.4)	0.589
Enteritis	0	1 (0.9)	1
Prostatitis	1 (4.5)	0	0.165
Subcutaneous fluid collection	1 (4.5)	0	0.165
Postoperative stay (days) (range)	12.4 (7–34)	12.6 (3–50)	0.875

All continuous variables are described as mean with range

similar incidence for the expert and novice surgeons. There were no cases of conversion to open surgery, positive circumferential margin, anastomotic leakage, or 30-day mortality.

Correlations between operative outcomes and clinical factors, as determined by univariate analysis, are summarized in Table 4. Gender (p=0.004), BMI (p<0.001), tumor location (p<0.001), and experience of the primary surgeon (p=0.004) were significantly associated with operative time; BMI (p=0.030), tumor location (p=0.042), and tumor size (p=0.019) were significantly associated with blood loss; age (p=0.040), tumor size (p=0.001), tumor depth (p=0.001), and tumor stage (p=0.010) were significantly associated with postoperative hospital stay; and tumor size (p=0.001), tumor depth (p=0.001), tumor stage (p=0.013), and extent of lymph node dissection (p=0.012) were significantly associated with the number of retrieved lymph nodes. Multivariate analysis showed that male gender (p=0.002), higher BMI (p<0.001), location of the tumor in the rectosigmoid colon (p<0.001), greater tumor depth (p=0.011), and operation by trainees (p<0.001) were independently predictive of longer operative time; higher BMI (p=0.040) and larger tumor size (p=0.025) were independently predictive of greater blood loss; larger tumor size was also related to longer postoperative stay (p=0.001) and a greater number of retrieved lymph nodes (p=0.001) (Tables 5 and 6).

Discussion

Laparoscopic resection for colorectal cancer is one of the most advanced laparoscopic procedures. Yet, lymph node dissection along the surgical trunk (right-sided colon cancer)

Table 4 Corrations between surgical outcomes and clinical factors

Independent variable	P value for operative outcomes			
	Operative time	Blood loss	Postoperative stay	Retrieved LN (<12 vs. ≥12)
Gender	0.004	0.311	0.226	0.096
Age	0.472	0.428	0.040	0.350
Body mass index	<0.001	0.030	0.411	0.163
Previous abdominal surgery	0.495	0.176	0.451	0.569
Tumor location (sigmoid vs. rectosigmoid)	<0.001	0.042	0.141	0.985
Tumor size	0.489	0.019	0.001	0.001
Tumor depth (Tis/T1/T2 vs. T3/T4)	0.322	0.081	0.001	0.001
Tumor stage (0/I/II vs. III/IV)	0.489	0.155	0.010	0.013
Experience of the primary surgeon (expert vs. trainee)	0.004	0.264	0.437	0.052
Lymph node dissection (D3/D2)	0.461	0.293	0.279	0.012

LN lymph nodes

Table 5 Stepwise linear regression analysis

Dependent variable	Predictive factor	*P* value	*β*	*R*	Model utility test
Operative time	Intercept	0.001		0.613	<0.001
	Tumor location (rectosigmoid)	<0.001	0.348		
	Body mass index	<0.001	0.345		
	Experience of the primary surgeon (trainee)	<0.001	0.261		
	Gender (male)	0.002	0.222		
	Tumor depth	0.011	0.189		
Blood loss	Intercept	0.056		0.252	0.014
	Tumor size	0.025	0.193		
	Body mass index	0.040	0.176		
Postoperative hospital stay	Intercept	<0.001		0.276	0.001
	Tumor size	0.001	0.276		

and around the root of middle colic vessels (transverse colon cancer) is still technically challenging [14]. Splenic flexure mobilization—required for tumors located in the left transverse or descending colon—is also reported to be difficult and time-consuming [15]. Pelvic procedures during rectal cancer resection, including rectal mobilization, transection, and anastomosis, are quite demanding in narrow and deep surgical fields. Moreover, they are associated with some disadvantages such as long operative time [4, 16, 17] and increased rate of positive surgical margins [6]. Meanwhile, laparoscopic ileocecal resection, sigmoid resection, and rectosigmoid resection are considered comparatively basic among all laparoscopic colorectal procedures. Therefore, laparoscopic training for surgical residents often begins with these procedures. In our institution, 83.3 % of all laparoscopic colorectal resection cases for sigmoid colon and rectosigmoid cancer (130/156) are performed by trainees at their initial laparoscopic training. These operations provide the trainees with sufficient experiences in advanced laparoscopic procedures and enable the development of their surgical techniques. Herein, we evaluated the impact of the operation by trainees on the short-term outcomes of laparoscopic resection for sigmoid and rectosigmoid cancer and determined the characteristics of patients suitable for operation by novice surgeons. We excluded cases of Hartmann's procedure and simultaneous resection of other organs such as the liver. These cases tend to correlate with longer operative time, greater blood loss, and/or longer hospital stay. Therefore, these cases should be analyzed independently of sigmoid or rectosigmoid resection and anastomosis in order to clearly distinguish the clinical factors that influence the operative outcomes of the latter.

In this study, multivariate analyses showed that operation by trainees was significantly associated with longer operative time. However, it had no negative impact on any of the other short-term outcomes evaluated in the current study. Furthermore, male gender, higher BMI, location of the tumor in the rectosigmoid, and greater tumor depth were significantly associated with longer operative time. The present findings are valuable in supporting the early introduction of laparoscopic resection for sigmoid and rectosigmoid cancer during the initial training period of novice surgeons. In addition, our findings indicate that female patients with a low BMI, sigmoid cancer, and/or shallow tumor depth are suitable for operation by trainees. Additionally, multivariate analyses showed that higher BMI and larger tumor size were independently predictive of greater blood loss; larger tumor size was also related to longer postoperative stay, indicating that larger tumors should best be managed by expert surgeons.

In our surgical training program, we pay special attention to safety and quality. These parameters were reflected in the careful selection of patients for operation by trainees. As such, trainees operated on significantly smaller tumors with significantly higher incidence of shallow depth to avoid oncologic impairments during the resection of advanced cancers. We usually consider that small tumors with shallow depth do not require wide lymph node dissection (D3

Table 6 Stepwise logistic regression analysis

Dependent variable	Predictive factor	*P* value	Odds ratio	95 % CI
Retrieved lymph nodes (<12 vs. □12)	Tumor size	0.001	1.556	1.193–2.029
Postoperative complication	No parameter			

dissection) as compared to advanced tumors [12, 18]. In the case of the former, it is decided preoperatively that D2 lymph node dissection, including only local and intermediate nodes, will be performed with dividing the SRA or the SA at its origin. This may explain the significant differences in the extent of lymph node dissection between expert and novice surgeons. In the current study, we performed multivariate analyses to eliminate the influence of these differences in patients' characteristics between the expert and the trainees; thus, we assume that the impact of primary surgeons was evaluated successfully without bias.

In this study, we have focused on colorectal cancer regional nodal evaluation—reported as a staging measure, prognostic variable, and quality indicator. A minimum of 12 nodes is endorsed as a consensus standard for hospital-based performance by the American Society for Clinical Oncology, the National Comprehensive Cancer Network, and the American Joint Committee on Cancer [19]. Twelve or more lymph nodes (mean, 19.0) were retrieved from 86 of 111 patients (77.5 %) operated on by trainees, and D3 lymph node dissection was performed in 70 patients (63.1 %); deep tumors (T3/T4) were observed in 55 patients (49.5 %), and positive nodes in 42 patients (37.8 %). Lymph node removal achieves two objectives in oncologic procedures: therapeutic effect and adequate nodal staging. With regard to the therapeutic effect, we assume that the number of lymph nodes retrieved by trainees was enough considering the not so high incidence of advanced tumors. Furthermore, the expert surgeon ensured that the trainees removed all lymph nodes together with mesocolon included within the preoperatively planned area during the operation. Therefore, we assume that trainees satisfied the oncologic principles suggested by the Japanese Society for Cancer of the Colon and Rectum [12], which do not recommend a minimum number of retrieved lymph nodes but rather a wider area of dissection compared to the Western guidelines [22] for assuring complete lymph node removal irrespective of their number, although these principles have been criticized as excessive [21]. Aside from the therapeutic effect of lymph node removal, it is commonly assumed that stage migration is reflected in the positive association between survival and the number of lymph nodes retrieved. Recently, analysis of the pathological staging of 131,953 patients from the Surveillance, Epidemiology and End Results database by a beta-binomial model suggested that the minimum number of nodes required for adequate nodal staging depends on the T stage: to achieve a probability of correct staging of 90 %, a single node needs to be examined for T1, four nodes for T2, 13 nodes for T3, and 21 nodes for T4 disease [23]. Based on this staged classification, the quality of lymph node removal by trainees would be acceptable for nodal staging of patients with the highest incidence of shallow tumors compared to those performed by the expert surgeon. The incidence of patients from whom less than 12 lymph nodes were retrieved was higher in surgeries performed by trainees, yet the difference was not statistically significant. An important factor, which could account for the difference in the number of lymph nodes retrieved, is that trainees performed a significantly higher number of D2 lymph node dissection than the expert. In fact, D2 lymph nodes dissection has been reported to yield fewer lymph nodes for histopathological examination than D3 lymph node dissection [20, 21]. The higher incidence of D2 lymph node dissection was attributable to the significantly higher incidence of shallow tumor depth in cases of operation by trainees because of the aforementioned reason; therefore, the higher incidence of patients with less than 12 retrieved lymph nodes could be associated with our policy of careful patient selection for operation by trainees. Multivariate analysis did not identify operation performed by trainees, but tumor size as an independent predictor of the number of retrieved lymph nodes.

Tumor size was also an independent predictor of postoperative hospital stay and blood loss. The relation between longer postoperative stay and larger tumor size is not very clear. Some patients with large tumors had poor general condition and required postoperative rehabilitation or transfer to other hospitals, which may explain the longer postoperative stay. Greater blood loss in patients with larger tumors may result from the greater difficulty in intra-abdominal laparoscopic handling along with a more limited surgical field. Significant association between greater tumor depth and longer operative time may be explained similarly: deeply invasive tumors require careful intra-abdominal manipulation to prevent intra-operative oncologic impairment such as tumor cell spillage.

Significant association between rectosigmoid cancer (as opposed to sigmoid cancer) and longer operative time, as well as between male gender and longer operative time suggests the influence of pelvic diameters. Previous reports showed that resection of low rectal tumors in males is usually performed through a narrower pelvic space. This anatomical constraint limits the working space and directly increases the difficulty in safe and quick access while minimizing visibility and retraction, thereby resulting in a significantly longer operative time [24–26]. Similar relationships may influence the outcomes of sigmoid and rectosigmoid colon cancer. Another reason for longer operative time in male patients may be the presence of greater abdominal visceral fat deposits in men than in women [27]. Higher BMI was also significantly associated with longer operative time and greater blood loss, yet the BMI of our patients were lower than that of Western populations. The latter observation is in agreement with our previous report on laparoscopic anterior resection for rectal cancer [24].

In this study, the overall morbidity rate was 6.8 % (9/133). Six of the patients had wound infections. Adverse events such as anastomotic leakages, conversions, positive circumferential margin, and 30-day mortality were not observed or occurred at a very low rate. This indicates that the procedure can be performed by the trainees in a safe way and in the absence of morbidity or violation of oncologic surgical principles. We believe that the assistance of the expert surgeon was essential to maintain the quality and safety of operations by trainees, providing good laparoscopic view with adequate retraction in the surgical field.

Nevertheless, our study has certain limitations. Operative outcomes, including complications, anastomotic leakage, conversion, mortality, and positive circumferential margin, should be examined to generalize the present findings. Moreover, this study only analyzed the short-term outcomes, and long-term follow-up is required to ensure that oncological procedures were not compromised.

In conclusion, this study identified operation by trainees as an independent risk factor for longer operative time but with no negative impact on any of the other short-term outcomes. Female patients with a low BMI, sigmoid cancer, shallow tumor depth, and/or small tumor are suitable for operation by trainees.

Competing interests The authors declare that they have no competing interests.

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●原　著●

ステージⅢ大腸癌に対する術後補助化学療法としてのカペシタビン（Xeloda®）内服療法の検討

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Oral Capecitabine as Postoperative Adjuvant Chemotherapy in Stage Ⅲ Colon Cancer Patients: Takashi Yamaguchi[*1], Meiki Fukuda[*1], Hisateru Yasui[*2], Shunsuke Okazaki[*2], Kimiyo Kubo[*3], Masako Tanaka[*3], Yoshiko Une[*4], Yuki Setoguchi[*4], Keita Hanada[*1], Sayaka Moriyama[*1], Masaki Tani[*1], Takahide Murakami[*1], Yoshihisa Okuchi[*1], Satoshi Ogiso[*1], Hiroaki Hata[*1], Shingo Sakata[*1], Tetsushi Otani[*1], Toshio Yamato[*1] and Iwao Ikai[*1] ([*1]*Dept. of Surgery*, [*2]*Dept. of Medical Oncology*, [*3]*Dept. of Nursing, and* [*4]*Dept. of Pharmacy, National Hospital Organization Kyoto Medical Center*)

Summary

Capecitabine (Xeloda®) has been a global standard drug for the treatment of colon cancer since large randomized controlled trials demonstrated its efficacy and safety in treating patients suffering from the disease. Few studies have been conducted to assess the effects of oral capecitabine treatment on Japanese patients. Therefor, we conducted this study to evaluate oral capecitabine as postoperative adjuvant chemotherapy in 50 patients who underwent surgery for stage Ⅲ colon cancer at our department. Patients received an 8 courses treatment with capecitabine during the study, and the incidence of adverse events, treatment completion rate, and treatment compliance were assessed. Adverse events were reported in a total of 46 patients (92%). The most common adverse event was hand-foot syndrome (HFS), reported in 39 patients (78%), whereas bone-marrow toxicity and diarrhea were reported in as few as 2 (4%) and 3 (6%) patients, respectively. Both these events were mild in severity, and no patients required hospitalization, nor were they associated with treatment-related deaths. The median treatment duration was 8 courses ranging from 3 to 8 courses, and the 8 courses treatment completion rate was 96%. The relative dose intensity, which was used as a treatment compliance index, is expressed as the actual dose taken by the patient divided by the dose planned at baseline. The median and mean of the relative dose intensity were 100% (ranging from 37% to 100%) and 93%, respectively. The results of this study showed that the safety profile of oral capecitabine therapy was generally favorable, with a lower incidence and lesser severity of life-threatening bone-marrow toxicity and diarrhea, although the treatment is still associated with frequent HFS. This is the great advantage of capecitabine when it is used as postoperative adjuvant chemotherapy for gastrointestinal cancer. Indeed, a satisfactory treatment completion rate was achieved in this study while maintaining a sufficient dose and treating HFS, by reducing the dose, interrupting treatment, or providing appropriate corrective measures. **Key words**: Capecitabine, Colon cancer, Adjuvant chemotherapy (*Received Aug. 16, 2011/Accepted Dec. 5, 2011*)

要旨　カペシタビン（Xeloda®）は大規模無作為比較試験により有効性と安全性が証明され，大腸癌治療における世界的標準治療薬となっている。本邦におけるカペシタビンの使用成績の報告は少ないため，当院にてステージⅢ大腸癌術後補助化学療法としてカペシタビン内服療法を行った50例の有害事象の発現状況，8コース治療完遂割合，内服コンプライアンスを評価した。有害事象の発現は46例（92%）に認められた。hand foot syndrome（HFS）が39例（78%）と高頻度であった一方，骨髄毒性は2例（4.0%），下痢は3例（6.0%）と頻度が低く症状も軽度であり，入院加療を要した症例や治療関連死亡は認めなかった。投与コースの中央値は8コース（3～8コース），8コース治療完遂割合は96%であった。内服コンプライアンスの指標として用いた相対用量強度（実内服量/治療開始時予定投与量）の中央値は100%（37～100%），平均は93%であった。

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カペシタビン内服療法は高頻度のHFSというデメリットがあるものの，骨髄毒性や下痢の頻度が低く，また軽度であり，安全性が高かった。消化管術後の補助化学療法という観点からは特筆すべき長所であり，HFSを適切な処置・休薬・減量で対処することで十分な投与量を保ちながら高い治療完遂率を得ることができた。

はじめに

大腸癌治療ガイドラインではステージⅢ大腸癌に対する術後補助化学療法として5-FU/LV静注療法やUFT/LV内服療法，カペシタビン（Xeloda®）内服療法が推奨されている[1]。本邦における大腸癌の術後補助化学療法は，歴史的に5-FU系内服抗癌剤が簡便性を理由に科学的検証なく頻用されてきたが，近年の欧米での大規模無作為比較試験により内服抗癌剤の有用性が証明され，エビデンスに基づいた治療法となった。カペシタビン内服療法はステージⅢ結腸癌術後補助化学療法の第Ⅲ相比較試験であるXeloda in adjuvant colon cancer therapy（X-ACT）試験において，5-FU/LV静注療法と比較して主要評価項目である5年無病生存期間の非劣性が証明され，優越性に関しても境界領域の結果が得られた[2]。5年無再発生存期間においては有意な改善がみられ，さらには主要な有害事象の発現率が低く，より安全性が高いことも示された。この結果を受けて長らく内服抗癌剤治療を好まなかった欧米において，5-FU/LV静注療法とともにカペシタビン内服療法が5-FU系の新たな標準治療と位置付けられた[3]。治療効果と安全性の点で最も評価されたカペシタビンが，本邦においてもステージⅢ大腸癌術後補助化学療法の標準治療薬と考えられ，当院では2007年12月の保険承認以降使用してきた。本邦における補助化学療法におけるカペシタビンの安全性や継続可能性についての報告は少ないため，ステージⅢ大腸癌術後補助化学療法としてカペシタビン内服療法を行った症例の有害事象の発現状況，8コース治療完遂割合，内服コンプライアンスを評価した。

Ⅰ．対象・方法

2008年2月～2010年10月までに，根治度Aの切除が行われたステージⅢ大腸癌の補助化学療法としてカペシタビン内服療法を行った患者のうち，ECOGのperformance status（PS）が0または1で主要臓器機能が保たれており，かつ治療の理解が十分得られた50例を対象とした。対象年齢の上限は設けなかった。カペシタビンの経口投与は2,500 mg/m^2/日に基づき設定された1日錠数を朝・夕食後の2回に分け，2週間連続投与の後，1週間休薬の3週間を1コースとした。大腸癌術後補助化学療法の標準的施行期間は6か月間であり，今回の検討でもX-ACT試験と同様に合計8コース投与（＝治療期間24週）を治療完遂と定義した。有害事象の判定は有害事象共通用語規準v 3.0日本語訳JCOG/JSCO版（CTCAE v 3.0）に従った。hand foot syndrome（HFS）のグレーディングに迷うことがあるが，その場合には低いグレードに判定した。グレード2以上の有害事象発現時には，基本的にカペシタビン適正使用ガイドの休薬・減量規定に従ったが，患者の希望や医師の判断も加味して適宜休薬・減量を行った。また，75歳以上の高齢かつPS1であった6例のうち，4例は開始時より1段階以内の減量を行った。内服コンプライアンスとして，相対用量強度（実内服量/治療開始時予定投与量）を用いた。

Ⅱ．結　果

患者背景を表1に示した。年齢の中央値は68歳（34～84歳），75歳以上の高齢者は13例（26%）であり，PS0が40例（80%），PS1が10例（20%）であった。病期はステージⅢaが37例（74%），ステージⅢbが13例（26%）であった。

有害事象の発現状況を表2に示した。HFSが39例（78%）と高頻度であった一方，骨髄毒性は2例（4%），下痢は3例（6%）と頻度が低かった。グレード3の有害事象はHFS 2例と血小板減少1例の合計3例（6%）であった。グレード3のHFS 2例中1例は2段階減量により8コース治療を完遂でき，1例は治療継続の理解が得られず中止となった。グレード3の血小板減少の1例は1週間の休薬にて改善し，1段階の減量により8コース治療完遂が可能であった。グレード4の有害事象はなく，入院加療を要した症例や治療関連死亡は認められな

表1　患者背景（n=50）

性別	男性	26例（52%）
	女性	24例（48%）
年齢	中央値	68歳
	範囲	34～84歳
	高齢者（75歳以上）	13例（26%）
ECOG	PS 0	40例（80%）
	PS 1	10例（20%）
病期	ステージⅢa	37例（74%）
	ステージⅢb	13例（26%）

ECOG: eastern cooperative oncology group
PS: performance status
病期：大腸癌取扱い規約第7版による

表 2 有害事象 (n=50)

	グレード1	グレード2	グレード3	全グレード
HFS	29例 (58%)	8例 (16%)	2例 (4%)	39例 (78%)
食欲不振	10例 (20%)	1例 (2%)	—	11例 (22%)
高ビリルビン血症	1例 (2%)	4例 (8%)	—	5例 (10%)
味覚障害	5例 (10%)	—	—	5例 (10%)
結膜炎	2例 (4%)	2例 (4%)	—	4例 (8%)
下痢	1例 (2%)	2例 (4%)	—	3例 (6%)
口内炎	2例 (4%)	1例 (2%)	—	3例 (6%)
悪心	2例 (4%)	—	—	2例 (4%)
好中球減少	—	1例 (2%)	—	1例 (2%)
血小板減少	—	—	1例 (2%)	1例 (2%)
肝機能異常	—	1例 (2%)	—	1例 (2%)

HFS: hand foot syndrome

表 3 カペシタビン投与状況 (n=50)

8コース治療完遂症例		48例 (96%)
減量を要した症例		12例 (24%)
治療開始時予定投与量	中央値	2,384
(mg/m^2/日)	範囲	1,879〜2,683
	平均	2,395
実内服量	中央値	2,295
(mg/m^2/日)	範囲	1,006〜2,661
	平均	2,231
相対用量強度	中央値	100%
	範囲	37〜100%
	平均	93%

相対用量強度: 実内服量/治療開始時予定投与量

表 4 治療中止・減量の主原因となった有害事象

中止	グレード3	HFS	1例
(2例)	グレード2	HFS	1例
	グレード3	HFS	1例
	グレード3	血小板減少	1例
	グレード2	HFS	3例
減量	グレード2	肝機能異常	1例
(12例)	グレード2	ビリルビン高値	1例
	グレード2	下痢	1例
	グレード2	口内炎	1例
	グレード1	複合因子	3例

表 5 治療開始時予定投与量とHFSの関係 (n=50)

	≧2,500 mg/m^2/日 (n=17)	<2,500 mg/m^2/日 (n=33)	p値
HFS (全グレード)	16例 (94%)	23例 (69%)	p=0.07
HFS (グレード2以上)	9例 (52%)	2例 (6%)	p=0.004

p値: χ^2検定 (Fisher両側検定)

かった。また, 8コース途中での再発は認められなかった。

投与状況を表3に示した。投与コースの中央値は8コース(3〜8コース), 8コース治療完遂例は48例(96%)であった。規定以外の休薬を要した症例は20例(40%), 減量を要した症例は12例(24%)であった。治療開始時予定投与量の平均は2,395 mg/m^2/日 (1,879〜2,683 mg/m^2/日) で, 実内服量の平均は2,231 mg/m^2/日 (1,006〜2,661 mg/m^2/日) であった。内服コンプライアンスの指標として用いた相対用量強度 (実内服量/治療開始時予定投与量) の中央値は100% (37〜100%), 平均は93%であった。

治療中止・減量の主原因となった有害事象を表4に示した。複数の有害事象が原因となっている場合は中止・延期の判断に最も影響を及ぼしたものを記載した。中止の2例はHFSを主とする有害事象の発現により, 治療継続の理解が得られず減量する前に中止となった。グレード1の有害事象で減量した3例は高齢など有害事象以外の因子も含めて考慮し, 継続性を重視した症例であった。

治療開始時投与量とHFSとの関連性について表5に示した。基準投与量である2,500 mg/m^2/日を境界として, 2,500 mg/m^2/日以上の高用量群17症例と2,500 mg/m^2/日未満の低用量群33症例におけるHFS発現率はそれぞれ94%, 69%と高用量群で高い傾向にあったが, 有意差は認めなかった (p=0.07)。一方, グレード2以上のHFS発現率はそれぞれ52%, 6%と高用量群で有意に高かった (p=0.0004)。

Ⅲ. 考　察

大腸癌治療ガイドラインではステージⅢ大腸癌に対する術後補助化学療法として，2010年版より5-FU系薬剤単独に加え，オキサリプラチン併用療法も推奨療法に加わった。しかし，その対象選択に当たっては本邦における良好な手術成績を勘案し，生存期間の上乗せ効果のみならず，有害事象および医療コストを十分に考慮すべきとされている[1,4]。われわれはステージⅢbをはじめとする再発高リスク症例に対して，年齢やPSなどを考慮しオキサリプラチンの適応を個別に判断している。また，欧米ではオキサリプラチン併用療法が第一に推奨され高頻度に行われているものの，高齢者，特に75歳以上においては補助化学療法そのものが20～30%以下にしか行われておらず，内容も5-FU系単剤療法が中心となっている[5,6]。したがって，補助化学療法における5-FU系単剤療法は世界的にみても未だ中心的治療法であり，高齢者やPSの悪い症例に使用されることも多く，また，手術後早期に治療開始となる点からも安全性が非常に重要となる。とりわけ問題となるのは生命を脅かす可能性のある骨髄毒性や腸管毒性である。カペシタビンは骨髄毒性や腸管毒性の軽減を意図して開発された薬剤であり[7]，実際X-ACT試験においてもカペシタビン療法の骨髄毒性，下痢はそれぞれ全グレード（グレード3/4）で32%（2%），46%（11%）と5-FU/LV静注療法の63%（26%），64%（13%）に比べて有意に発現頻度が低いことが示された[2]。本邦では，大腸癌に対するカペシタビンの使用経験が浅く安全性の報告は少ないが，須藤らにより47例のステージⅢ大腸癌術後補助化学療法としてのカペシタビンの使用経験が報告されている[8]。骨髄毒性，下痢は全グレードにおいてそれぞれ12%，4%と低く，グレード3以上の毒性は認めなかった。自験例でも骨髄毒性，下痢は全グレードで4%，6%と発現は低頻度であり，グレード3以上の毒性としては血小板減少1例（2%）のみであった。経口フッ化ピリミジン薬剤の毒性に人種差があることは報告されているが[9]，須藤らの報告や自験例における骨髄毒性と下痢はX-ACT試験より大幅に低い頻度であり，欧米諸国に比して本邦ではカペシタビンがさらに安全に投与できることが示唆された。また，大腸癌ガイドラインにおけるもう一つの推奨補助化学療法であるUFT/LV内服療法はNSABP C-06試験で下痢を74%（グレード3は29%）[10]，本邦における角田らの99例の検討では下痢を33%（グレード3は6%）に認めた[11]。UFT/LV内服療法においても日本人では下痢の発現頻度が低かったが，それでも33%の下痢を認め，そのうちグレード3が6%でほとんどが入院加療を要したことを考えると，同一試験での比較ではないことを勘案してもカペシタビン療法の腸管毒性の少なさは際立っているといえる。その結果として，カペシタビン療法の8コース治療完遂率はX-ACT試験で83%，須藤らの報告で90%，自験例では96%といずれも同様に高かった。治療開始時投与予定量の平均は2,395 mg/m²/日であることからも十分な投与量設定であり，実内服量の平均は2,231 mg/m²/日で相対用量強度（実内服量/治療開始時予定投与量）の平均は93%と高く，高い完遂率のみならず減量の必要性が少なく，実際に十分量の投与が可能であったことが示された。

カペシタビン療法を継続する上で問題となるのはHFSである。X-ACT試験でのHFSは全グレードで60%，うちグレード3が17%，須藤らの報告ではそれぞれ87%，6.4%，自験例では78%，4%であり，いずれの検討でも高頻度に認めている。HFSは骨髄毒性や腸管毒性と異なり，生命を脅かすことはないため過小評価しがちであるが，苦痛が強くなれば内服コンプライアンスの低下につながるため，適切な管理にてquality of life（QOL）を維持する必要がある。自験例ではグレーディングに迷った場合は低いグレードに判定し，安易な休薬や減量を行わなかったが，治療中止に至った2例はいずれもHFSのために治療継続の理解が得られなかった症例であった。HFSが発現するコースの中央値は2コースで，全例5コース以内と比較的早期から発現することが多いため，化学療法開始時からのビタミンB_6や保湿剤の投与および日常生活における手足のケアが大切であり，外来看護師や薬剤師の協力も得て患者指導を行うことが望ましい。HFSの悪化を認める際には早めに皮膚科での受診を促し，比較的軽症のうちに対処して重症化を防ぐことが肝要である。QOLや完遂率の向上のみを求めるような安易な休薬・減量は避けるべきであるが，X-ACT試験においてもカペシタビン減量時の治療効果への影響は認められず[12]，継続可能な適正用量に休薬・減量することも重要である。

経口剤の欠点として，体表面積に従った添付文書の錠数設定では基準投与量2,500 mg/m²/日を中心に開始時投与量が2,300～2,700 mg/m²/日の範囲でばらつきが生じる。自験例において，開始時投与量が2,500 mg/m²/日以上となる高用量群は2,500 mg/m²/日未満の低用量群に比べ，HFS発現率が有意差はないものの高い傾向にあり，グレード2以上のHFS発現率は高用量群で有意に高かった。治療を完遂できず中止となった2例についても，開始時投与量は2,500 mg/m²/日を超えていた。UFT/LV内服療法におけるコンプライアンスでも同様の報告がみられ，Meguroらは大腸癌術後補助化学療法

で，UFT/LV 内服開始時の体表面積当たりの投与量が多い症例では内服コンプライアンスが有意に悪いことを示した[13]。カペシタビンは服用する錠数が多く内服しづらいといわれることがあるが，逆に 1 錠ずつの減量により，投与量を大幅に落とすことなく，きめ細かな用量設定が可能になるという利点を有するととらえることもできる。添付文書の設定錠数が体表面積当たりどれぐらいの量に相当するのかを計算し，基準の 2,500 mg/m^2/日より高用量になる場合は年齢，PS，腎機能など他の投与量調整因子とともに検討し，初期からの減量や HFS 発現時に早めの減量を考慮するなど工夫を行うことも必要である。

カペシタビン療法は高頻度の HFS というデメリットがあるものの，腸管毒性が低いことは特筆すべき長所であり，消化管術後という観点からも非常に使いやすい利点を有しているといえる。また，カペシタビン療法は欧米や本邦で効果や安全性のみならず，医療経済学的にも優れていることが示され[14,15]，大腸癌術後補助化学療法における 5-FU 系標準治療薬と考えられる。本邦において行われているステージⅢ大腸癌補助化学療法に関する大規模試験として，JCOG0205（5-FU/LV 静注療法と UFT/LV 内服療法の比較），JCOG0910（カペシタビン内服療法と S-1 内服療法の比較），ACTS-CC（UFT/LV 内服療法と S-1 内服療法の比較）[16]がある。これら 5-FU 系薬剤どうしの効果や有害事象の比較の最終結果が得られるまでは，標準治療であるカペシタビン内服療法を実地臨床において安全に使いこなすことが重要である。骨髄毒性や腸管毒性など重篤な有害事象が少なく安全であることを基盤として，高頻度に起こる HFS を適切な処置・休薬・減量で対処することで，十分な投与量と QOL のバランスを保ちながら治療完遂することが可能である。

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