






ORIGINAL ARTICLE

Institutional variation in survival and morbidity in laparoscopic surgery for colon cancer: From the data of a randomized controlled trial comparing open and laparoscopic surgery (JCOG0404)

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Abstract

Background: Institutional variation in outcomes is a key factor to ascertain the generalizability of results and reliability of the clinical trial. This study evaluated institutional variation in survival and postoperative complications using data from JCOG0404 comparing laparoscopic colectomy (LAP) with open colectomy (OP).

Methods: Institutions with fewer than 10 registered patients were excluded from this analysis. Institutional variation was evaluated in terms of early postoperative complications, overall survival, and relapse-free survival and estimated using a mixed-effect model with institution as a random effect after adjusting for background factors.

Results: This analysis included 1028 patients in the safety analysis and 1040 patients in the efficacy analysis from 26 institutions. In the safety analysis, there was no variation in grades 3–4 early postoperative complications (in OP, median 6.3% [range 6.3%–6.3%]; in LAP, median 2.6% [range 2.6%–2.6%]), but some variation in grades 1–4 early postoperative complications was observed (in OP, median 20.8% [range

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13.2%–31.8%]; in LAP, median 11.9% [range 7.2%–28.7%]), and that in grades 2–4 was observed only in LAP (median 8.8% [range 4.7%–24.0%]; in OP, median 12.7% [range 12.7%–12.7%]). Two specific institutions showed especially high incidences of postoperative complications in LAP. In the efficacy analysis, there was no institutional variation in OP, although a certain variation was observed in LAP.

Conclusions: Some institutional variations in safety and efficacy were observed, although only in LAP. We conclude that a qualification system, including training and education, is needed when new surgical techniques such as laparoscopic surgery are introduced in clinical practice.

KEYWORDS

colon cancer, institutional variation, laparoscopic surgery, open surgery, randomized controlled trial

1 | INTRODUCTION

Hospital volume and surgeon volume are known to be associated with short-term and long-term outcomes in the surgical treatment of some types of cancer. The greater the number of hospitals and surgeons involved in a trial, the wider the range of quality of surgical treatment.¹ As institutional variation in the quality of surgery may affect the results of a surgical trial, quality control and quality assurance are key factors when conducting such trials. Additionally, as surgical outcomes may depend on the skill of the surgical team, learning curves and variations in technique and in quality of surgery must be assessed and controlled.² Assessments of the generalizability of the results and reliability of a surgical trial revealed institutional variation in short-term and long-term outcomes after surgery in some types of cancer.^{3–5}

Randomized controlled trials (RCTs) comparing laparoscopic surgery with open surgery for colorectal cancer patients have been conducted worldwide.^{6–9} The Colorectal Cancer Study Group of the Japan Clinical Oncology Group (JCOG) conducted JCOG0404, a multicenter RCT, to confirm the noninferiority of laparoscopic surgery to open surgery for patients with stage II/III colon cancer (registered at ClinicalTrials.gov, number NCT00147134, and in UMIN-CTR, number C000000105). In JCOG0404, only surgeons qualified by the study chair performed both types of surgery, as an operator or instructor, to ensure surgical quality. Nearly at the same time as the initiation of JCOG0404, the Japan Society for Endoscopic Surgery (JSES) developed its Endoscopic Surgical Skill Qualification System (ESSQS) in 2004, and the number of surgeons certified by JSES-ESSQS as well as the number of laparoscopic operations had been increasing during the study period.^{10,11} Consequently, the ratio of annual operation volume between open surgery and laparoscopic surgery for colorectal cancer varied among institutions. In fact, more than half of the participating hospitals mainly performed open surgery for stage II/III colorectal cancer in clinical practice at that time. There was no information on whether the learning curve had reached the plateau phase in each participating hospital or whether the surgical performance

had stabilized at the level of expertise, even though the qualification system had been introduced in JCOG0404. Whether a qualified surgeon performed surgery as an operator or instructor depended on the institutions; thus, we needed to evaluate institutional variation not only in laparoscopic surgery but also in open surgery.

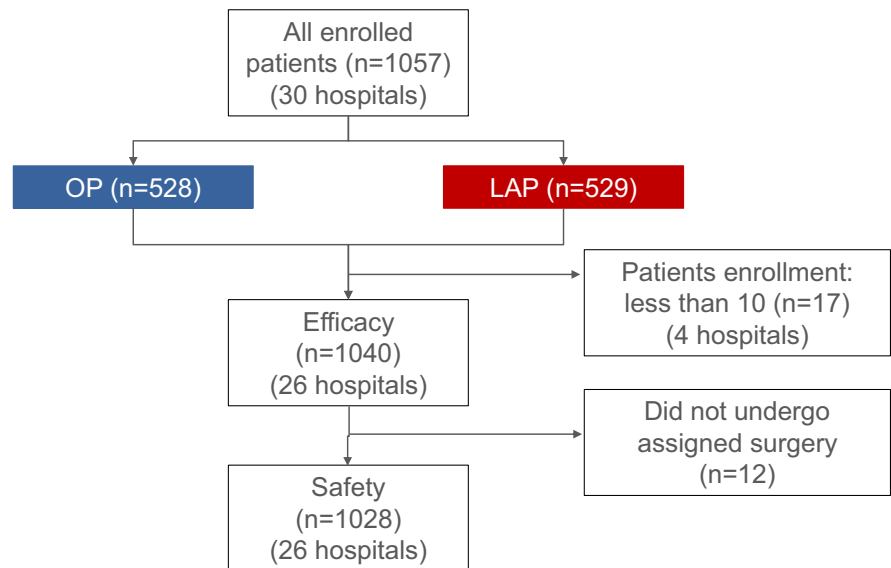
The impact of hospital volume on outcomes in laparoscopic surgery for colorectal cancer patients has been reported.^{12,13} However, there is no report on institutional variation in outcomes in open and laparoscopic surgery in patients with colorectal cancer. Because JCOG0404 was conducted during a transitional period from open to laparoscopic surgery for stage II/III colorectal cancer, it is important to assess the quality of surgery, such as the selection of participating hospitals, surgeon qualification, and central review of the surgical procedure; this will be informative for future surgical trials. Therefore, the aim of this study was to evaluate institutional variation in postoperative complications for safety and overall survival (OS) and relapse-free survival (RFS) for efficacy using data from JCOG0404. Additionally, we examined the correlation between short-term and long-term outcomes and institutional factors.

2 | METHODS

2.1 | Summary of JCOG0404

Patients with colon carcinoma located in the cecum, ascending colon, sigmoid colon, or rectosigmoid colon and clinically diagnosed as having T3-4/N0-2/M0 lesions without involvement of other organs based on colonoscopy and abdominopelvic computed tomography (CT) were eligible for the trial. Patients were randomized to open or laparoscopic surgery preoperatively, and they underwent colectomy with D3 lymph node dissection in both approaches. Postoperative chemotherapy with the Roswell Park regimen of 5-fluorouracil (500 mg/m² by bolus infusion on d 1, 8, 15, 22, 29, and 36) and l-leucovorin (250 mg/m² by 2-h drip infusion on d 1, 8, 15, 22, 29, and 36) was administered for patients with pathological stage III disease.

FIGURE 1 Analyzed population



The primary endpoint was OS, and the secondary endpoints were RFS, short-term clinical outcomes, adverse events, and proportion of conversion from laparoscopic surgery to open surgery. For surgical quality assurance, only qualified surgeons (30 open colectomies in open, 30 open and 30 laparoscopic colectomies in laparoscopic) participated in this trial, and they performed surgery as an operator or instructor. In addition, intraoperative photographs were taken for all patients, and a video of randomly selected patients was recorded for a central review of the surgical procedures. The results of the central review were provided to the participating hospital, and the key points were shared among all participating hospitals. This RCT was approved by the Clinical Trial Review Committee of JCOG and the Institutional Review Board of each participating hospital. Written informed consent was obtained from all patients before enrollment. This RCT was conducted between October 2004 and March 2009 in Japan. In total, 1057 patients were enrolled from 30 hospitals in Japan. The details of this study and the results of short-term surgical outcomes have already been published.^{14,15} The results of JCOG0404 showed that the noninferiority of laparoscopic D3 lymph node dissection with respect to OS was not demonstrated, possibly due to unexpectedly better OS in both arms. However, the OS of both arms was over 90%; therefore, laparoscopic surgery is considered an acceptable treatment option for patients with stage II/III colon cancer.⁹

2.2 | Outcomes in this study

Among 1057 patients from 30 participating hospitals in JCOG0404, 17 patients from four hospitals were excluded because the number of patients enrolled in these hospitals was <10 (required for efficacy analysis), and 12 patients who did not undergo assigned surgery were excluded from the safety analysis. The endpoints of this study were OS and RFS for efficacy and proportion of early postoperative complications for safety. OS was estimated from the date of enrollment

until death from any cause. RFS was defined as the time from randomization to relapse or death from any cause or to the last date on which the relapse-free status was confirmed. Surviving patients and patients who were lost to follow-up were censored at the latest contact date. The proportion of early postoperative complications corresponded to the frequency of patients who experienced any of the following postoperative complications: anastomotic leak ("Leak-large bowel"), small bowel obstruction ("Obstruction-colon and small bowel"), ileus, wound complication ("Wound complication, noninfectious" and "Infection with normal absolute neutrophil count-wound"), and urinary tract infection ("Infection with normal absolute neutrophil count-urinary tract"). Early postoperative complications from the completion of an operation to the first discharge were counted and described according to the Common Terminology Criteria for Adverse Events 3.0 (Table S1).¹⁶ Correlations between those estimated outcomes and institutional factors were also estimated. Institutional factors included the number of open and laparoscopic surgeries performed during patient enrollment in each hospital and the number of qualified surgeons by JSES in 2009. This supplementary analysis was a post-hoc analysis and was performed in accordance with the international ethical recommendations stated in the Declaration of Helsinki and the Japanese Ethical Guidelines for Clinical Research.

2.3 | Statistical analysis

Variation among hospitals was estimated by a generalized mixed-effect model with institution as a random effect after adjusting for age, sex, comorbidity, tumor location, body mass index (BMI), and clinical stage. A logistic regression model was used for binomial outcomes, and the Cox regression model was used for time-to-event outcomes. The associations between the estimated outcomes and hospital/surgeon volume were evaluated by Spearman's correlation coefficients. All statistical analyses were performed with SAS v. 9.2 or higher (SAS Institute, Cary, NC).

3 | RESULTS

The patient flow diagram of this study is shown in Figure 1. For efficacy analysis, 1040 patients (519 in the open arm and 521 in the laparoscopic arm) from 26 hospitals were analyzed, and for safety analysis, 1028 patients (511 in the open arm and 517 in the laparoscopic arm) from 26 hospitals were analyzed.

The results of baseline characteristics for efficacy are shown in Table 1. Age, sex, main tumor location, and BMI are well-balanced between the arms. The number of stage II patients was smaller and the number of stage III patients was larger in the laparoscopic arm than in the open arm. Table 2 summarizes the operative findings and early postoperative complications. The operation time was 52 min longer in the laparoscopic arm, but the amount of blood loss was 55 mL less in the laparoscopic arm. The proportions of type of surgery, type of anastomosis, and reoperation were similar in both arms. The proportion of grades 1–4 early postoperative complications was 21.9% (grade 1/2/3/4:8.4%/6.8%/6.5%/0.2%, respectively) in the open arm and 14.5% (grade 1/2/3/4:2.5%/8.1%/3.9%/0%, respectively) in the laparoscopic arm. The collected data of institutional factors are shown in Figure 2. The medians for the number of enrollments in JCOG0404, number of certified surgeons by JSES in 2009, and number of open and laparoscopic surgeries performed during the period of enrollment in JCOG0404 were 35.5, 2, 486.5, and 375.5, respectively.

Figure 3A–C show the institutional variation in estimated proportion of grades 1–4, 2–4, and 3–4 early postoperative complications,

respectively. There was no institutional variation in estimated proportion of grades 3–4 early postoperative complications (Figure 3C). As shown in Figure 3A, there were 112 grades 1–4 events in the open arm and 75 in the laparoscopic arm. The range of the estimated proportion of grades 1–4 complications was from 13.2%–31.8% in the open arm and from 7.2%–28.7% in the laparoscopic arm. There were two outliers only in the laparoscopic arm. The percentages of these outliers were 21.5% and 28.7%. As shown in Figure 3B, the median and range of the estimated proportion of grades 2–4 complications were 12.7% (12.7%–12.7%) in the open arm. On the other hand, the median and range of the estimated proportion of grades 2–4 complications were 8.8% (4.7%–24.0%) in the laparoscopic arm. Again, there were two outliers only in the laparoscopic arm; the percentages of these outliers were 19.6% and 24.0%.

Figure 4A,B show institutional variation in estimated 5-y OS and 5-y RFS, respectively. The median and range of estimated 5-y OS were 92.0% (92.0%–92.0%) in the open arm and 92.0% (87.9%–95.4%) in the laparoscopic arm. The median and range of estimated 5-y RFS were 81.9% (81.9%–81.9%) in the open arm and 80.8% (69.9%–89.6%) in the laparoscopic arm. There was no institutional variation in estimated 5-y OS and 5-y RFS in the open arm. However, there was some institutional variation in estimated 5-y OS and a greater extent of institutional variation in estimated 5-y RFS in the laparoscopic arm.

The correlation between estimated outcomes and institutional factors is shown in Table 3. There were no factors that essentially influenced the outcomes.

TABLE 1 Baseline characteristics

	OP N = 519	LAP N = 521
Age (median, range)	64 (33–75)	64 (28–75)
Sex		
Male	308 (59.3%)	280 (53.7%)
Female	211 (40.7%)	241 (46.3%)
Co-morbidity		
Yes	278 (53.6%)	292 (56.0%)
No	241 (46.4%)	229 (44.0%)
Main tumor location		
Cecum	55 (10.6%)	43 (8.3%)
Ascending	95 (18.3%)	109 (20.9%)
Sigmoid	232 (44.7%)	245 (47.0%)
Rectosigmoid	137 (26.4%)	124 (23.8%)
BMI (median, range)	22.7 (14.0–40.9)	22.9 (14.8–36.1)
Clinical stage		
Stage II	361 (69.6%)	326 (62.6%)
Stage III	156 (30.1%)	194 (37.2%)
Stage IV	2 (0.4%)	1 (0.2%)

Abbreviations: BMI, body mass index; LAP, laparoscopic colectomy; OP, open colectomy.

4 | DISCUSSION

JCOG0404 is one of the largest RCTs in the world comparing open colectomy to laparoscopic colectomy for patients with colon cancer. In this trial, the proportion of severe (grades 3–4) early postoperative complications and the proportion of conversion to open surgery were low, and treatment-related death did not occur because the quality control of surgery in both arms was well performed. However, the present analysis showed that there was some degree of institutional variation in the estimated proportion of grades 1–4 early postoperative complications in both arms, in that of grades 2–4 early postoperative complications, and in estimated RFS in the laparoscopic arm. There was a higher proportion of estimated grades 1–4 and 2–4 early postoperative complications in two specific institutions in the laparoscopic arm.

The results were contrary to our expectations. Our hypothesis in this study was that there was little institutional variation in either arm or, if any, that there was some institutional variation in the open arm, because it was assumed that experienced surgeons performed laparoscopic surgery as an operator but performed open surgery as an instructor. The biggest influencing factor of institutional variation in estimated proportion of grades 1–4 and 2–4 early postoperative complications was wound-related complications (“wound complication, noninfectious” and “infection with normal absolute neutrophil

TABLE 2 Operative findings and early postoperative complications

	OP N = 511	LAP N = 517
Operation time (min) (Median, range)	160 (70-710)	212 (97-616)
Blood loss (mL) (Median, range)	85 (0-3395)	30 (0-4080)
<100 mL	271	424
≥100 mL	240	93
Type of surgery		
Ileocecal resection	52 (10.2%)	34 (6.6%)
Partial resection	4 (0.8%)	7 (1.4%)
Right hemicolectomy	95 (18.6%)	109 (21.1%)
Sigmoidectomy	204 (39.9%)	228 (44.1%)
Low anterior resection	153 (29.9%)	137 (26.5%)
Hartmann's procedure	1 (0.2%)	0 (0%)
Others	2 (0.4%)	2 (0.4%)
Type of anastomosis		
Hand-sewn	42 (8.2%)	39 (7.5%)
Functional end-to-end	147 (28.8%)	144 (27.9%)
Circular staple	310 (60.7%)	321 (62.1%)
Others	11 (2.2%)	13 (2.5%)
Missing	1 (0.2%)	0 (0%)
Reoperation	13 (2.5%)	9 (1.7%)
Grade 1-4 early postoperative complications	112 (21.9%)	75 (14.5%)
Wound-related complications	51 (10.0%)	28 (5.4%)
Anastomotic leak	18 (3.5%)	19 (3.7%)
Paralytic ileus	18 (3.5%)	16 (3.1%)

Abbreviations: LAP, laparoscopic colectomy; OP, open colectomy.

count-wound"). In clinical practice, the same case could be classified to either grade 1 "wound complication, noninfectious" or grade 2 "infection with normal absolute neutrophil count-wound." In short, institutional variation in the estimated proportion of grades 1-4 and 2-4 early postoperative complications may have been associated with a type of reporting bias. As for two specific institutions in the laparoscopic arm, the number of open and laparoscopic surgeries during patient enrollment, including the cases not enrolled in JCOG0404, was more than the median number, and there were two JSES-certified surgeons in each institution. Thus, a lack of experience was not the reason for the high proportion of postoperative complications.

Regarding the institutional variation in efficacy, if there had been institutional variation in both arms, this could have been explained by the difference among institutions in factors such as postoperative chemotherapy, follow-up imaging examinations, or recurrence diagnosis. In fact, there was institutional variation in estimated RFS only in the laparoscopic arm. In particular, the estimated RFS in the three institutions with poor outcomes in the laparoscopic arm was about 10%

lower than the median estimated RFS in the open arm. Among these three institutions, only one institution overlapped with two specific institutions regarding early postoperative complications. In these institutions, the number of patients enrolled in JCOG0404 was larger than the median number of enrolled patients, and there was at least one qualified surgeon; however, the number of open surgeries performed in clinical practice during patient enrollment was larger than the number of laparoscopic surgeries performed in all of these institutions. In particular, the number of laparoscopic surgeries was the smallest in one institution. Although the surgical procedure was standardized, including that for lymph node dissection, and almost all patients underwent D3 dissection, the level of experience with laparoscopic surgery might have affected the institutional variation in estimated RFS.

Quality control of surgery is important for conducting a surgical trial. The Dutch Gastric Cancer Group trial (Dutch D1D2 trial) failed to demonstrate the benefit of extended lymph node dissection for gastric cancer because of higher morbidity and mortality in the D2 dissection arm.¹⁷ The expert gastric cancer surgeon from Japan who instructed participating surgeons reported several critical issues in running surgical trials: specific training and standardization to perform the surgical procedure, defining procedural details, conducting regular monitoring, and setting termination rules, among others.¹ The selection of participating hospitals is also important when conducting a surgical trial. Before JCOG0404 was started, JCOG conducted some surgical trials and recognized quality control of surgery as a key point for the success of a clinical trial. Therefore, qualification of participating surgeons and central review of the surgical procedure were introduced in JCOG0404. In addition, the steering committee of the JCOG0404, comprising the study chair, the study coordinator, and some experts in both open and laparoscopic colorectal surgery, selected experienced hospitals based on objective information such as the annual number of operations. After JCOG0404 was started, the ESSQS for colorectal surgery was introduced by the JSES, and the number of laparoscopic colorectal surgeries and surgeons certified by JSES-ESSQS has increased in Japan. The JSES-ESSQS is a skill accreditation by an academic body. The certified surgeons are required to have the skills not only to complete common laparoscopic surgery safely and appropriately by their own efforts but also to train beginners and medical staff. Sufficient experience of laparoscopic surgery (at least 20 cases) and technical assessment based on an unedited video of a surgical procedure performed by the applicant are required to obtain the JSES-ESSQS certification.^{18,19} Although the certification by JSES-ESSQS was not mandatory in JCOG0404, there was at least one JSES-ESSQS certified surgeon who performed surgery as an operator or instructor in almost all institutions. This certification system played a key role in improving the quality of not only laparoscopic but also open surgery.

Although laparoscopic surgery for colorectal cancer has been recommended worldwide, including in Japan, we must recognize that there is some institutional variation in terms of short-term and long-term outcomes of laparoscopic surgery compared with open surgery. We believe that a surgeon certification system and a central review and feedback system for surgical procedures by recording intraoperative

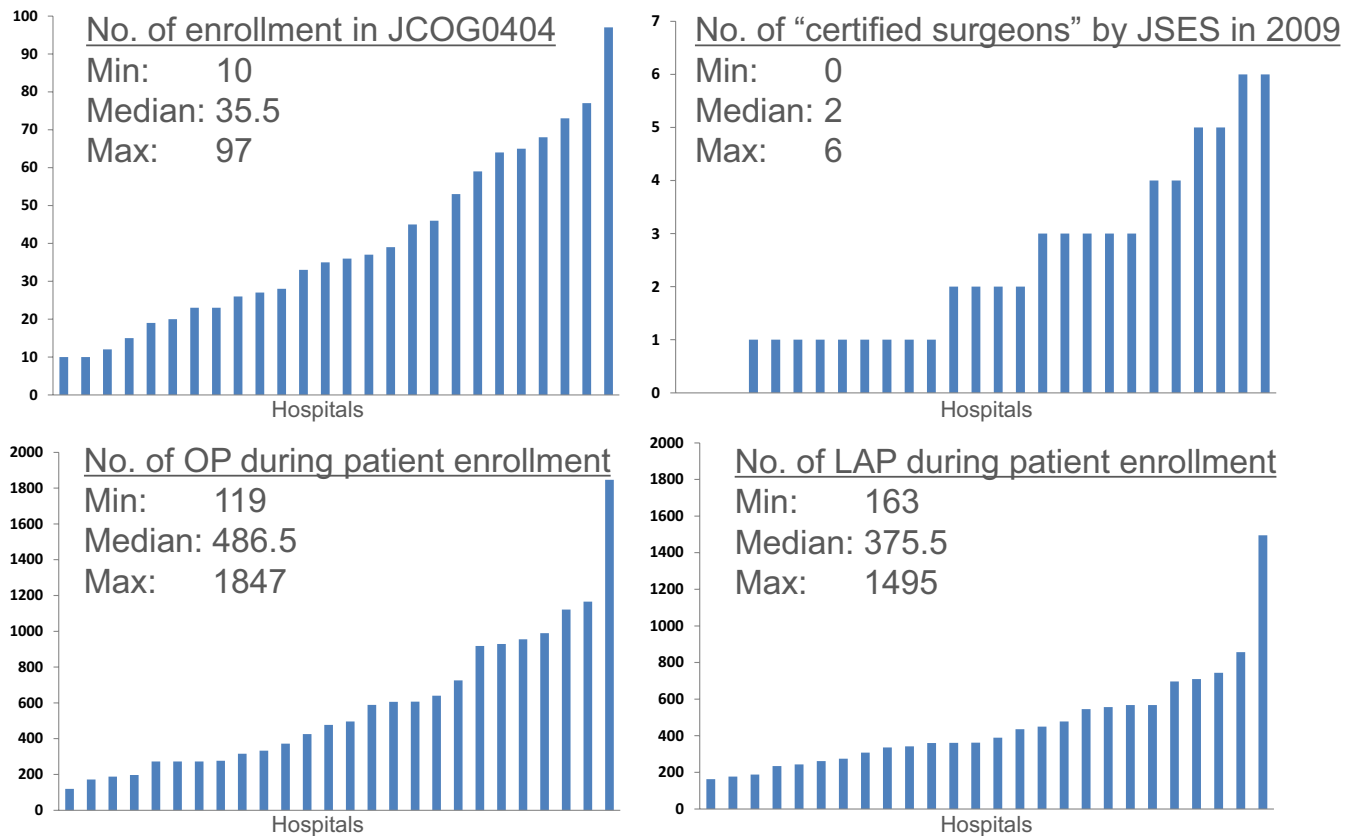


FIGURE 2 Institutional factors

surgical videos in addition to photographs after lymph node dissection are important to minimize the institutional variation. Additionally, there is an urgent need to identify factors associated with institutional variation, such as hospital volume, the number of surgeons at each hospital, and participation of certified surgeons. To maintain and improve the quality of laparoscopic surgery, the training and education system conducted by JSES has spread in Japan. However, it might become essential to educate surgeons more effectively and ensure that laparoscopic surgery is properly performed across the country.

Regarding whether surgical trial results are applicable to actual patients treated by general surgeons (generalizability of surgical trial results), two points need to be considered. One is how the surgical skill has matured in clinical practice when the surgical trial is started; the other is whether trial participants represent “real world” patients in clinical practice (representativeness). Although the results from this study did not show a generalizability of JCOG0404 results, another study using the data from JCOG0404 reported the representativeness or the generalizability of clinical trial results.²⁰ Unfortunately, their study results could not confirm the generalizability and representativeness of JCOG0404; therefore, careful consideration is needed when applying the results of JCOG0404 to patients in daily practice.

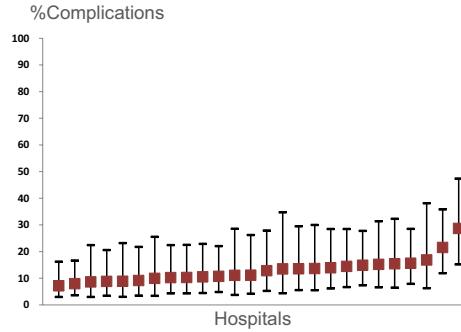
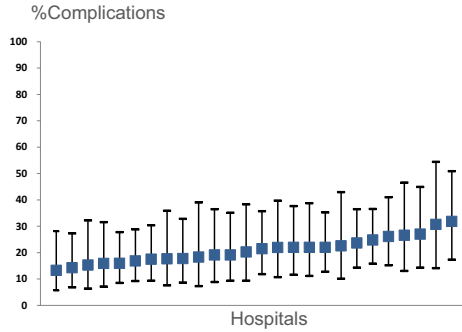
There are some limitations to this study. First, the data on whether a qualified surgeon performed as an operator or an assistant were not collected in JCOG0404. Thus, this study showed institutional variation but did not show variation among surgeons. Second, the methods used for the prevention of surgical site infection (SSI) possibly caused the institutional variation in the estimated proportion of grades 1–4 and 2–4 early postoperative complications. In most participating hospitals, bowel preparations were performed and preoperative antibiotics were used according to the clinical practice guidelines for appropriate use published by the Japan Society for Surgical Infection. These guidelines have been prepared by the modification of Centers for Disease Control and Prevention guidelines for SSI prevention to adapt them to Japanese clinical practice. However, the data on bowel preparations and perioperative antibiotic use were not collected; therefore, it is difficult to discuss the difference in the methods used for SSI prevention among participating hospitals. Finally, regarding the institutional variation in estimated RFS in the laparoscopic arm, there were some considerable causes. It was possible that the level of experience with laparoscopic surgery or lack of adherence to the follow-up imaging examination was the influencing factor, but unfortunately, detailed data were not collected.

FIGURE 3 (A) Institutional variation in grades 1–4 early postoperative complications. (B) Institutional variation in grades 2–4 early postoperative complications. (C) Institutional variation in grades 3–4 early postoperative complications

(A) Institutional variation in grades 1-4 early postoperative complications

OP n=511 (No. of events 112)

LAP n=517 (No. of events 75)

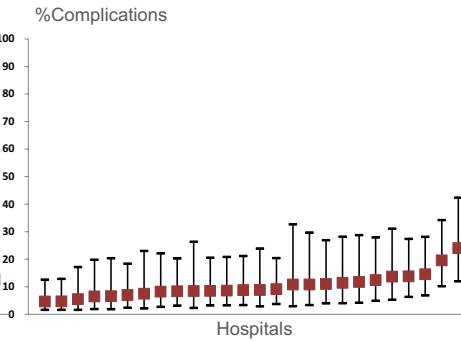
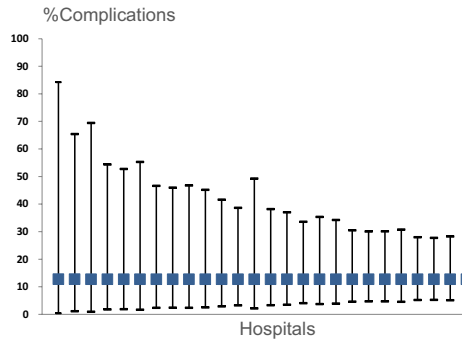


- %Complications – Median 20.8% (range 13.2-31.8%)
 - %Complications – Median 11.9% (range 7.2-28.7%)
- %Complications were estimated by Mixed effect model adjusting for patients background factors

(B) Institutional variation in grades 2-4 early postoperative complications

OP n=511 (No. of events 69)

LAP n=517 (No. of events 62)

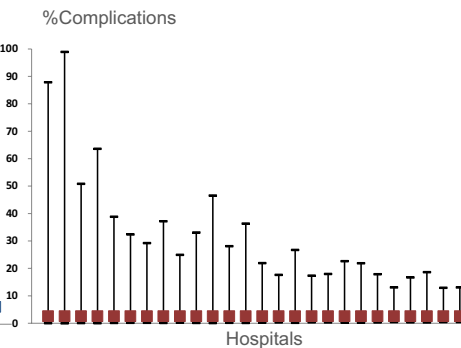
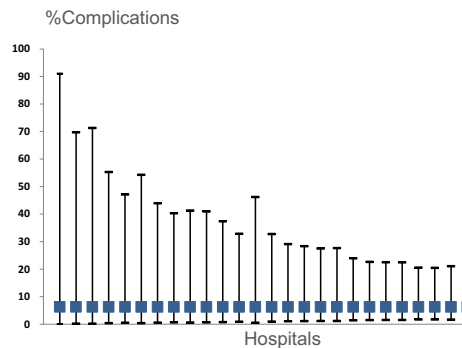


- %Complications – Median 12.7% (range 12.7-12.7%)
 - %Complications – Median 8.8% (range 4.7-24.0%)
- %Complications were estimated by Mixed effect model adjusting for patients background factors

(C) Institutional variation in grades 3-4 early postoperative complications

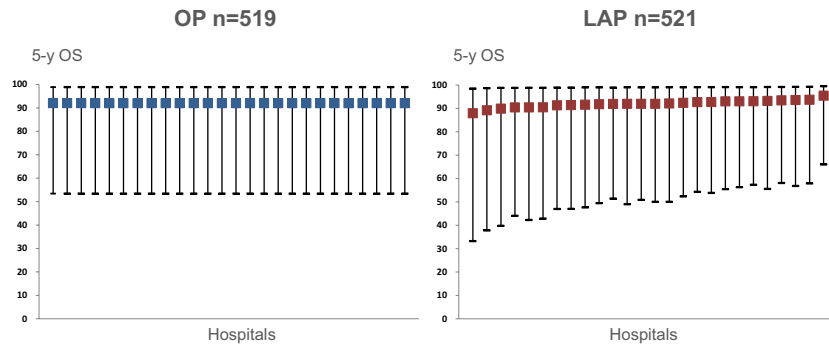
OP n=511 (No. of events 34)

LAP n=517 (No. of events 20)



- %Complications – Median 6.3% (range 6.3-6.3%)
 - %Complications – Median 2.6% (range 2.6-2.6%)
- %Complications were estimated by Mixed effect model adjusting for patients background factors

(A) Institutional variation in 5-y overall survival



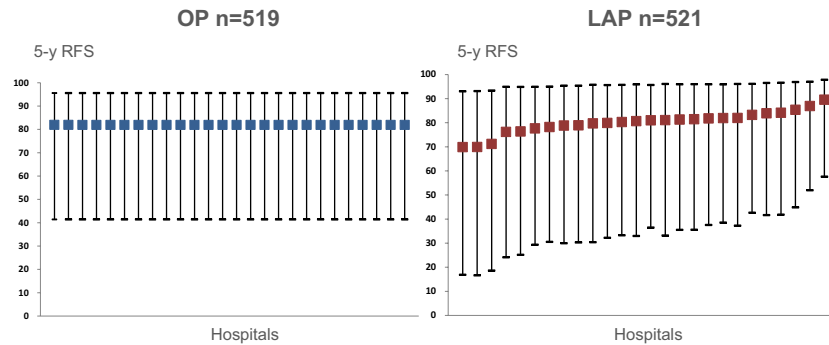
- OS – Median 92.0% (range 92.0-92.0%)
- OS – Median 92.0% (range 87.9-95.4%)

OS were estimated by Mixed effect model adjusting for patients background factors

FIGURE 4 (A) Institutional variation in 5-y overall survival. (B) Institutional variation in 5-y relapse-free survival

(B)

Institutional variation in 5-y relapse-free survival



- RFS – Median 81.9% (range 81.9-81.9%)
- RFS – Median 80.8% (range 69.9-89.6%)

RFS were estimated by Mixed effect model adjusting for patients background factors

TABLE 3 Correlation between the estimated outcomes and the institutional factors

	Grades 1-4 complication in OP	Grades 1-4 complication in LAP	OS in LAP	RFS in LAP
Number of enrollment in JCOG0404	$\rho = -.09$ (P value = .65)	$\rho = -.04$ (P value = .86)	$\rho = .33$ (P value = .10)	$\rho = .17$ (P value = .40)
Number of OP (2004-2009)	$\rho = .06$ (P value = .77)	$\rho = -.16$ (P value = .44)	$\rho = .11$ (P value = .62)	$\rho = .07$ (P value = .75)
Number of LAP (2004-2009)	$\rho = -.10$ (P value = .62)	$\rho = .02$ (P value = .92)	$\rho = .30$ (P value = .14)	$\rho = .26$ (P value = .20)
Number of qualified surgeons in 2009	$\rho = .10$ (P value = .65)	$\rho = .23$ (P value = .27)	$\rho = -.03$ (P value = .89)	$\rho = -.03$ (P value = .90)

Abbreviations: BMI, body mass index; LAP, laparoscopic colectomy; OP, open colectomy; OS, overall survival; RFS, relapse-free survival.

5 | CONCLUSION

Even though surgical quality control and assurance were performed in JCOG0404, institutional variation was observed in the open arm only in grades 1-4 early postoperative complications. However, in

the laparoscopic arm institutional variation was observed in grades 1-4 and 2-4 early postoperative complications and in 5-y RFS. Our interpretation of this analysis is that a qualification system, including training and education, is needed when new surgical techniques such as laparoscopic surgery are introduced in clinical practice.

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DISCLOSURE

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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