



Surgical starting time in the morning versus the afternoon: propensity score matched analysis of operative outcomes following laparoscopic colectomy for colorectal cancer

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Abstract

Background The number of colorectal cancer cases is increasing, and so the number of laparoscopic colectomy procedures being performed is also increasing, leading to an increased workload for surgeons. However, operating for prolonged time periods may cause surgeons to lose their concentration and develop fatigue. We hypothesized that there is a time-of-day variation in outcome for patients with colorectal cancer who undergo laparoscopic colectomy. The present study aimed to compare the operative outcome between laparoscopic colectomy for colorectal cancer performed in the morning versus the afternoon.

Methods This was a single-center, retrospective study. All 1961 consecutive patients who underwent laparoscopic surgery for colorectal cancer between 2007 and 2017 were included; 1006 of these patients underwent morning surgery, while 955 underwent afternoon surgery. These patients were analyzed using propensity score matching, giving 791 patients in each group. The short- and long-term outcomes in both groups were compared.

Results Before propensity score matching, the morning group had a larger mean tumor size than the afternoon group (30 cm vs 35 cm; $P=0.0035$). After matching, the two groups did not significantly differ in any patient characteristics. Compared with the afternoon group, the morning group had a significantly lesser incidence of intra-operative organ injury (0.25% vs 1.13%; $P=0.027$), and a significantly greater incidence of post-operative abdominal abscess (2.03% vs 0.75% $P=0.028$). The incidences of other complications and morbidities were similar in both groups. The median operative time in the morning group (201 min) was significantly longer than that in the afternoon group (193 min; $P=0.0124$). The two groups did not differ in 5-year overall survival rates and 5-year disease-free rates within any disease stage.

Conclusions Surgical start times are correlated with surgical outcomes. Our data will help to ensure the safest possible surgeries.

Keywords Colorectal cancer · Laparoscopic colectomy · Surgical starting time · Propensity match score

Colorectal cancer (CRC) is the third most commonly diagnosed malignancy, and the fourth leading cause of cancer-related deaths worldwide, and its burden is expected to increase by 60% to more than 2.2 million new cases and 1.1 million cancer deaths by 2030 [1, 2]. This increase in CRC incidence means that the number of colectomy procedures being performed is also increasing, increasing

surgeons' workloads. Long working hours may cause surgeons to lose concentration, and to experience sleep deprivation and fatigue. This fatigue can decrease surgical performance [3]. Previous research has shown that surgeon fatigue and concentration loss increase the number of intra-operative errors [3, 4]. Studies have suggested that the time-of-day at which a procedure is performed significantly impacts patient outcomes in general surgery, cardiac surgery, gynecology, orthopedics, and neurosurgery [5–8]. To the best of our knowledge, no previous study has evaluated the relationship between the time-of-day that surgery is performed and outcomes following laparoscopic colectomy for CRC. In the field of CRC, surgeons may perform two or three major operations each day. We hypothesized that

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the surgical outcome in patients undergoing laparoscopic colectomy for CRC would vary according to the time of the day at which surgery began; that is, that patients undergoing surgery in the morning would have better short- and long-term outcomes than those undergoing surgery in the afternoon. The aim of the present study was to compare the operative and survival outcomes of patients who underwent laparoscopic colectomy for CRC in the morning versus the afternoon.

Methods

Patient selection

This was a propensity score matched retrospective study. All 1961 consecutive patients who underwent laparoscopic surgery for CRC between 2007 and 2017 at our institution were included. These 1961 patients (1006 who underwent surgery in the morning, and 955 who underwent surgery in the afternoon; in the morning surgery and afternoon surgery, the same surgeon operated 110 cases (5.61%)) met the inclusion criteria for the present study, and were analyzed

using propensity score matching. Complete descriptions of patient and tumor characteristics are listed in Table 1. The main outcome measures were intra- and post-operative complications, duration of post-operative hospitalization, operating time, estimated bleeding volume, number of lymph nodes removed, rate of conversion to laparotomy, and survival outcomes. Additionally, data on patient age, sex, BMI, American Society of Anesthesiologists (ASA) score, previous abdominal surgery, medical co-morbidities, and TNM stage were retrospectively collected from the electronic medical records. The present study included patients of any age or sex who underwent laparoscopic colectomy for curative treatment of CRC. Exclusion criteria were stage 4 colon cancer, Chemoradiation therapy, recurrent cases, multiple cancers, and emergency surgery. The operative start time was categorized as either beginning before 1 p.m. (morning surgery) or after 1 p.m. (afternoon surgery). All cases were performed on a weekday (i.e., Monday to Friday). Post-operative morbidity and mortality were respectively defined as complications or death occurring within 30 days of surgery or during hospitalization. Post-operative complications were defined as those classified as grade 2 or above in accordance with the Clavien-Dindo system [9]. Intra-operative

Table 1 Characteristics before and after propensity score matching

	Overall			After matching		
	AM group (<i>n</i> = 1,006)	PM group (<i>n</i> = 955)	<i>P</i> value ^a	AM group (<i>n</i> = 791)	PM group (<i>n</i> = 791)	<i>P</i> value ^a
Age, years	67 (25–94)	68 (25–94)	0.91	67 (25–94)	67 (25–94)	0.54
Sex			0.76			0.51
Male	543 (53.9)	498 (52.1)		414 (52.3%)	427 (53.9)	
Female	463 (46.0)	457 (47.9)		377 (47.7)	364 (46.0)	
BMI, kg/m ²	22 (14–38)	22.6 (13–34)	0.39	22.6 (14.6–38.2)	22.4 (13.4–40.6)	0.33
ASA grade			0.58			0.53
1	749 (74.4)	689 (72.1)		590 (74.6)	577 (72.9)	
2	242 (24.1)	252 (26.4)		188 (23.8)	204 (25.8)	
3	15 (1.49)	14 (1.47)		13 (1.64)	10 (1.26)	
Prior surgeries	284 (28.2)	305 (31.9)	0.056	235 (29.7)	237 (29.9)	0.91
Tumor size, mm	30 (0–120)	34 (0–280)	0.0035	35 (0–110)	35.2 (0–110)	0.96
Tumor location			0.47			0.59
Right	350 (34.8)	356 (37.3)		280 (35.4%)	279 (35.3)	
Left	656 (65.2)	599 (62.7)		511 (64.6)	512 (64.7)	
Surgeon certification	672 (66.8)	550 (57.8)	0.00001	503 (63.6)	501 (63.3)	0.85
Pathological stage			0.76 ^b			0.65 ^b
I	425 (42.1)	364 (38.1)		319 (40.1)	325 (40.9)	
II	274 (27.2)	287 (30.0)		224 (28.3)	216 (27.6)	
III	307 (30.5)	304 (31.8)		248 (31.3)	250 (31.6)	

Values are given as median (range) or *n* (%)

AM group patients who underwent surgery that started before 1 p.m., PM group patients who underwent surgery that started after 1 p.m., ASA American Society of Anesthesiologists

^a*P* values calculated using Fisher's exact test

^b*P* values calculated using χ^2 test

complications were defined as those that required repair during the operation. Length of overall survival (OS) was defined as the time from surgery to the date of death from any cause. Disease-free survival (DFS) was defined as the time from surgery to the date of recurrence or death from any cause.

The study protocol was approved by the Ethics Committee of our institution, and conforms to the provisions of the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board for the Use of Human Subjects of our institution, and written informed consent was obtained from all patients prior to study inclusion.

Surgeon validation

The number of operative surgeons was 26. The surgeons were divided into two groups: one group who had obtained endoscopic surgical skill certification ($n=9$), and the other group who had not obtained this certification ($n=17$).

Surgical procedure

Each patient was placed in the supine position under general anesthesia. A 12-mm trocar for a 30° rigid electrolaparoscope was inserted through an umbilical incision using the open technique, with CO₂ pneumoperitoneum established and maintained at 10 mmHg.

Four additional trocars were introduced into the right-middle (5 mm), right-lower (5 mm), left-middle (5 mm), and left-lower (12 mm) quadrants of the abdomen. The camera port was expanded to extract the specimen through an incision of 3–5 cm. Using a median approach, right hemicolectomy was performed with initial peritoneal dissection between the mesoileum and retroperitoneum. Left hemicolectomy, sigmoidectomy, and anterior resection were achieved via a medial-to-lateral approach. After intact mesocolic plane resection performed with complete mesocolic excision to remove all potential routes of metastatic tumor spread, central vascular ligation was completed by dissecting the ileocolic, right colic, middle colic, and inferior mesenteric vessels at their origins, depending on the tumor location. The specimen was extracted through the umbilical incision.

Patient follow-up

All patients were followed up for survival. Recurrence and distant metastasis were diagnosed on the basis of blood tests, including carcinoembryonic antigen and carbohydrate antigen 19–9, and CT, endoscopy, MRI, and positron emission tomography-CT. Blood testing was performed every 3 months for 3 years post-operatively. CT was performed every 6 months

for 5 years post-operatively. Endoscopy was performed annually for 5 years post-operatively.

Propensity score matching

Laparoscopic colectomy comprised right hemicolectomy for cecal cancer and for right-sided ascending or transverse colon cancer; left hemicolectomy, sigmoidectomy, or anterior resection was performed for cancer of the left-sided descending, sigmoid, or rectosigmoid colon, and for rectal cancer. To minimize the effect of these differences in procedure and tumor location, we applied propensity score matching. Propensity scores were calculated for each patient with bivariate logistic regression on the basis of the following covariates: sex, age, BMI, ASA grade, tumor location, tumor size, TMN stage, proportion of surgeons with endoscopic surgical skill certification, and previous abdominal surgery. These propensity scores were used to match patients in the morning group in a 1:1 ratio with patients in the afternoon group. We applied the nearest available Mahalanobis metric matching within calipers defined by the propensity score (caliper=0.02).

Statistical analysis

Statistical analyses were performed using JMP Pro 10 software (SAS Institute, Cary, NC). Results are summarized as the means and standard deviations, or the medians and ranges for continuous variables; categorical variables are summarized as numbers and frequencies. Median and mean values were compared between groups by means of the Mann–Whitney test or the Chi square test in univariate analyses. All post-operative complications were analyzed using binary logistic regression. OS and DFS were analyzed using the Kaplan–Meier method, and between-group differences were evaluated by the log-rank test. P values of <0.05 were considered to indicate significant differences.

Sample size

The appropriate sample size was calculated based on the assumption of a difference of 13% in post-operative complications rates. This difference was considered relevant based on previous studies [10], and a sample size of 1918 patients (959 in the morning group and 959 in the afternoon group) was needed to prove this difference (α set at 0.05; β set at 0.2; power=80%).

Results

Characteristics before and after propensity score matching

Before propensity score matching, the morning group had a larger mean tumor size and the proportion of surgeons than the afternoon group ($P=0.0035$, 0.00001 Table 1). After matching, the two groups each included 791 patients, and did not significantly differ in any patient characteristics (Fig. 1; Table 1).

Peri-operative outcomes

Peri-operative outcomes are summarized in Table 2. The incidence of intra-operative organ injury was significantly lesser in the morning group than in the afternoon group ($P=0.03$). Intra-operative vascular injury did not significantly differ between the two groups. The morning group had a greater incidence of intra-peritoneal abscess than the afternoon group ($P=0.04$). The two groups did not significantly differ regarding the incidences of post-operative cardiovascular system complications, anastomotic leakage, wound infections, ileus, anastomotic bleeding and stenosis, pneumonia, enteritis, bleeding events, and mortality. The median operative time was shorter in the afternoon group compared with the morning group ($P=0.01$). The median bleeding volume, duration of post-operative hospitalization,

and rate of conversion to open surgery did not significantly differ between the morning and afternoon groups. The cardiovascular system complications included two cases of percutaneous coronary intervention for angina pectoris, and two cases of myocardial infarction.

Pathologic and oncologic outcomes

The pathologic and oncologic outcomes are summarized in Table 3. The morning and afternoon groups showed similar median distal resection margins; however, the median proximal resection margin was longer in the morning group compared with the afternoon group ($P=0.04$). There were no significant differences between groups regarding the median numbers of harvested lymph nodes, TNM stage, depth of invasion, and N classification.

Survival outcomes

After propensity score matching, the median follow-up duration in the morning group [36 months (range 0.5–60 months)] was similar to that in the afternoon group [36 months (range 0.5–60 months)]. The 5-year OS rates did not significantly differ between the two groups (Fig. 2). The two groups did not differ in 5-year OS rates within any disease stage (Fig. 2).

The 5-year DFS rates did not significantly differ between the two groups (Fig. 3). The two groups did not differ in 5-year DFS rates within any disease stage (Fig. 3).

Fig. 1 Flowchart of patient selection

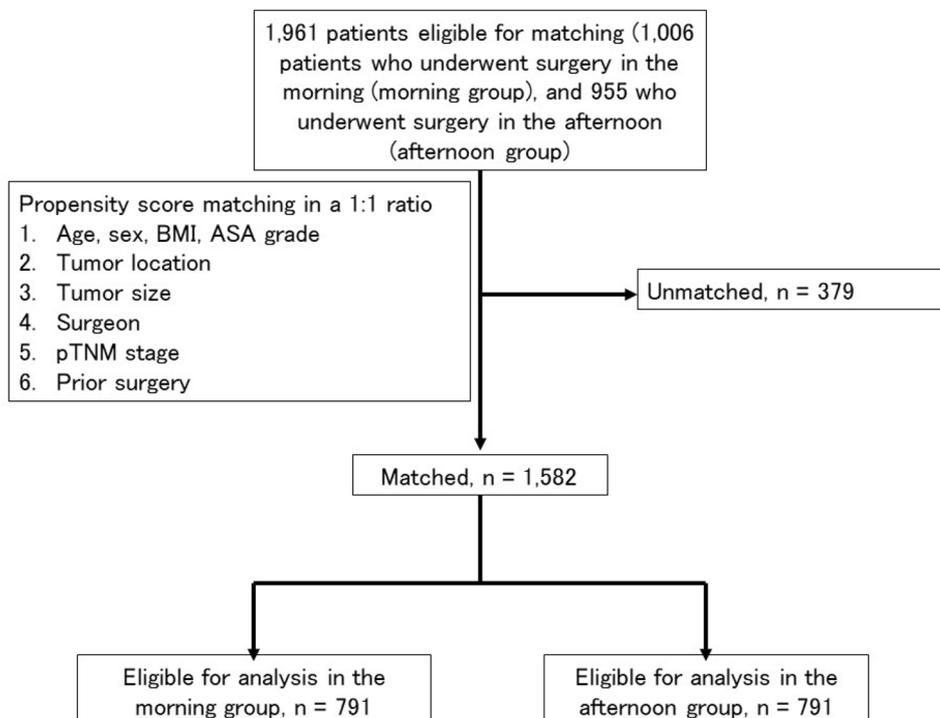


Table 2 Post-operative outcomes

Variable	AM group (<i>n</i> = 791)	PM group (<i>n</i> = 791)	<i>P</i> value ^a
Operative time, min	201 (55–298) ^b	193 (55–555) ^b	0.0 ^c
Bleeding volume, mL	70.6 (0–3270) ^b	65.6 (0–4141) ^b	0.46 ^c
Duration of post-operative hospitalization	11.2 (7–99)	11.3 (6–100)	0.98
Conversion to open surgery	2 (0.25)	2 (0.25)	1.00
Intra-operative complications	11 (1.39)	26 (3.29)	0.01
Vascular injury	8 (0.11)	12 (1.52)	0.37
Adjacent organ injury	2 (0.25)	9 (1.13)	0.03
Complications	76 (9.6)	79 (9.9)	0.80
Wound infection	17 (2.15)	14 (1.77)	0.59
Anastomotic leakage	17 (2.15)	18 (2.28)	0.87
Ileus	17 (2.15)	30 (3.79)	0.57
Intra-peritoneal abscess	16 (2.03)	6 (0.76)	0.03
Pneumonia	3 (0.37)	2 (0.25)	0.65
Enteritis	6 (0.76)	4 (0.50)	0.25
Perforation	3 (0.38)	3 (0.38)	1.00
Anastomotic bleeding	4 (0.50)	4 (0.50)	1.00
Anastomatic stenosis	1 (0.13)	4 (0.50)	0.16
Bleeding	10 (1.26)	6 (0.76)	0.32
Cardiovascular system	0 (0)	3 (0.38)	0.24
Mortality	2 (0.25)	1 (0.126)	0.57

Data are shown as *n* (%) unless otherwise Indicated

AM group patients who underwent surgery that started before 1 p.m., *PM group* patients who underwent surgery that started after 1 p.m.

^a*P* values calculated using Fisher's exact test

^bdata shown as median [range]

^c*P* values calculated using the Mann–Whitney *U* test

Table 3 Post-operative pathological outcomes

Variable	AM group (<i>n</i> = 791)	PM group (<i>n</i> = 791)	<i>P</i> value ^a
Depth of tumor, <i>n</i> (%)			0.63 ^d
Tis–T1	50 (6.32)	44 (5.56)	
T2	225 (28.4)	216 (27.3)	
T3	147 (18.4)	170 (21.5)	
T4	369 (46.7)	361 (45.6)	
N classification, <i>n</i> (%)			0.98 ^d
N0	340 (72.0)	332 (70.8)	
N1	98 (20.8)	116 (24.7)	
N2	27 (5.72)	17 (3.63)	
N3	7 (1.48)	4 (0.852)	
Proximal resection margin, cm	122 (13.5–290) ^b	117 (20–328) ^b	0.04 ^c
Distal resection margin, cm	87.5 (2–298) ^b	88.9 (2–276) ^b	0.56 ^c
Harvested lymph nodes	24 (0–82) ^b	24.2 (0–73) ^b	0.79 ^c

Data are shown as *n* (%) unless otherwise indicated

AM group patients who underwent surgery that started before 1 p.m., *PM group* patients who underwent surgery that started after 1 p.m.

^a*P* values calculated using Fisher's exact test

^bdata shown as median (range)

^c*P* values calculated using the Mann–Whitney *U* test

^d*P* values calculated using the χ^2 test

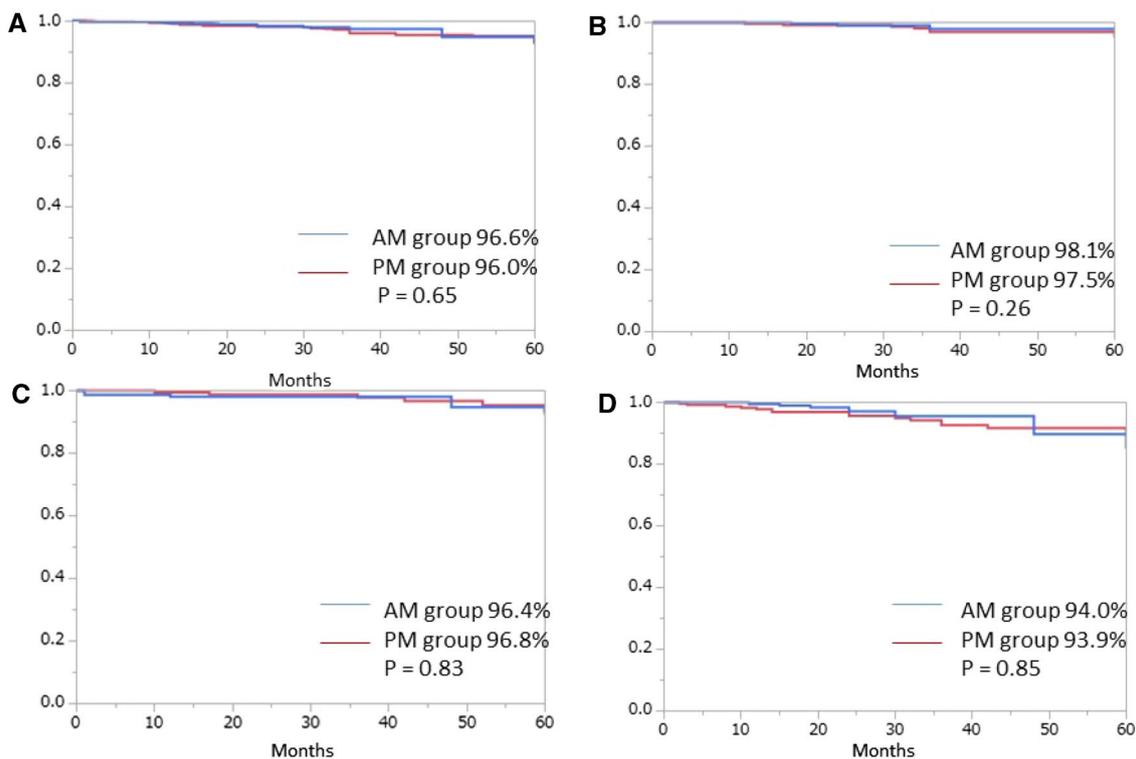


Fig. 2 Kaplan–Meier curves for 5-year overall survival (OS) among all patients (**A**), stage 0/1 patients (**B**), stage 2 patients (**C**), and stage 3 patients (**D**) after propensity score matching. Differences between the AM and PM groups were assessed by the log-rank test. *Ordinate*

survival rate, *abscissa* months after surgery, *AM group* patients who underwent surgery that started before 1 p.m., *PM group* patients who underwent surgery that started after 1 p.m.

Discussion

We hypothesized that surgeon fatigue and loss of concentration affected surgical performance, and that the surgical outcomes of afternoon surgery would be worse than those of morning surgery. The present study showed that afternoon surgery was associated with a significantly greater incidence of intra-operative complications than morning surgery. Furthermore, patients who underwent afternoon surgery had a shorter median operative time and a lower rate of intra-peritoneal abscess compared with those who underwent morning surgery. Hence, the present case-matched study showed that operative outcome was associated with surgical starting time. Regarding oncological outcomes, the median proximal resection margins were longer in the morning group compared with the afternoon group; however, there were no significant differences between the two groups in OS and DFS within any disease stage.

Theoretically, surgical fatigue could lead to careless technique, resulting in additional bleeding requiring reoperation. Furthermore, operative exhaustion may increase the tendency to overlook surgical bleeding. However, some previous studies have reported that operative outcomes do not depend on the starting time in general surgery, cardiac

bypass surgery, lung transplantation, and renal transplantation [11–14]. For both heart and lung transplants, the rate of cardiac reoperation was the same regardless of operative time-of-day, suggesting that the fatigue associated with night-time operations is not associated with poor surgical performance [13]. In contrast, Kelz et al. [6] reported that unadjusted later start time was significantly associated with greater surgical morbidity and mortality, and Linzey et al. [15] reported that the risk of morbidity was increased in surgeries performed from 9 p.m. to 9 a.m. Furthermore, Komen et al. [10] reported that after-hours construction of an anastomosis was an independent risk factor for colorectal anastomotic leakage in patients with CRC. Although this previous study found that other complications were not associated with surgical start time, it was focused on almost open surgery [10]. Performing laparoscopic surgery is more stressful for surgeons than performing open surgery [16]. Therefore, we hypothesized that the outcomes of laparoscopic surgery for CRC would be affected by surgeon fatigue, and excluded open surgery from the present study.

The quality of the performance of surgical tasks is reportedly reduced by surgeon body fatigue and sleep deprivation [17]. These disruptions prolong the rest phase, and present as exhaustion and fatigue in humans [18]. Consistent with past

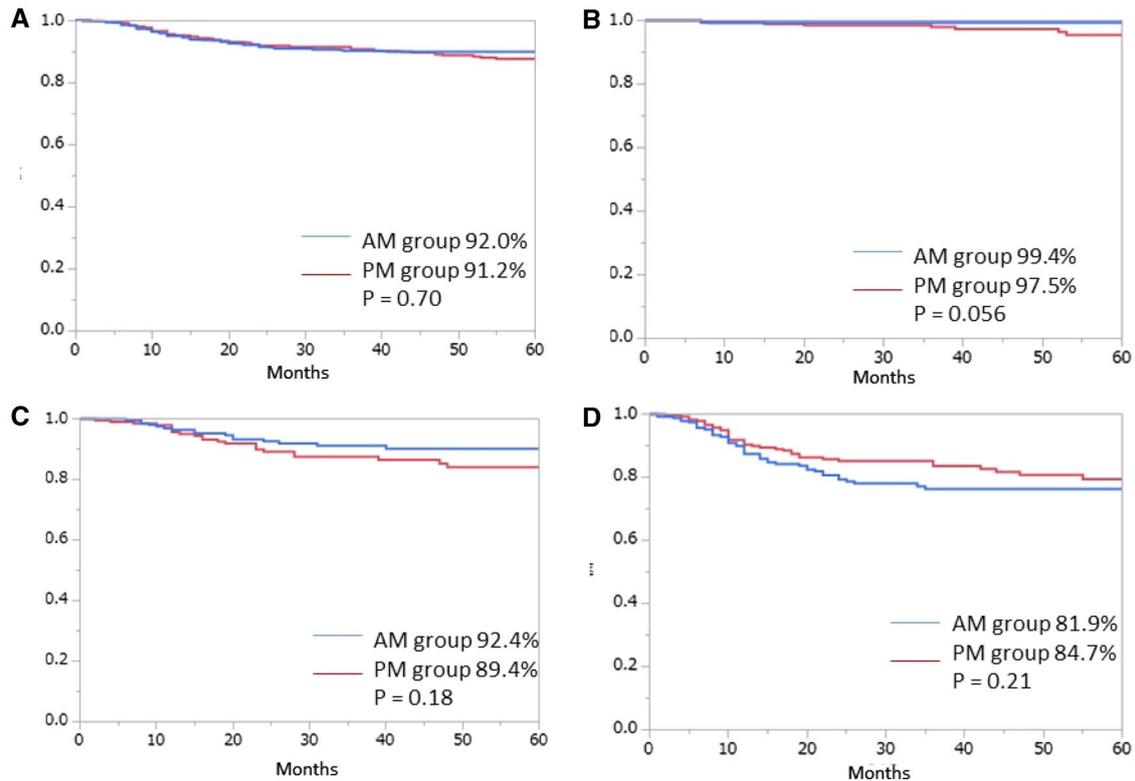


Fig. 3 Kaplan–Meier curves for 5-year disease-free survival (DFS) among all patients (A), stage 0/1 patients (B), stage 2 patients (C), and stage 3 patients (D) after propensity score matching. Differences between the AM and PM groups were assessed by the log-rank test.

Ordinate survival rate, *abscissa* months after surgery, *AM group* patients who underwent surgery that started before 1 p.m., *PM group* patients who underwent surgery that started after 1 p.m.

reports [3–8, 10, 15, 18], our results showed that the morning group had a greater incidence of intra-operative complications such as adjacent organ injury than the afternoon group. Furthermore, some small animal model studies have demonstrated that circadian regulatory mechanisms play an important role in both the humoral and innate immune responses [18–22]. Humans also have circadian variations in several acute illnesses, including ventricular tachyarrhythmia, myocardial ischemia/infarction, and stroke [18].

The current study showed that the median operative time was shorter in the afternoon group than in the morning group. This might be attributed to several factors that are difficult to confirm in a retrospective analysis; however, we suggest that surgeons may have more time in the morning compared with the afternoon, and so the operative time may be prolonged in the morning. Furthermore, those who underwent morning surgery had a significantly greater incidence of abdominal abscess than those who underwent afternoon surgery. There are two factors that may explain this finding: first, prolonged operative time is reportedly a risk for abdominal abscess [23, 24]; and second, the surgical outcomes may potentially have been affected by the present propensity score matching with eight clinical factors to reduce

patient selection biases. Although there are inevitable hidden selection biases due to unmatched variables, propensity score matching is a useful method for reducing selection bias between two groups, and contributed to the similar operative time between the two groups.

The current study is associated with some limitations. First, it was a retrospective and single-center study. Therefore, the possibility of unintentional selection bias in the selection of patients could not be fully excluded. Furthermore, as our hospital is a university hospital, there might have been an intentional treatment and possible hospital bias. Secondly, we did not evaluate nontechnical skill, which may be associated with peri- and post-operative outcomes. There may be a decrease during the night in the non-technical skills of the operating team, including teamwork, management skills, and situational awareness. Situational awareness (the ability of the surgeon to observe, understand, and predict events in the operating room) appears to be closely related to technical error rates [25]. In addition, the situational awareness, teamwork, and management skills of the anesthetists and nurses may have an important impact on the outcome of surgical patients [26]. Although we attempted to reduce selection bias by using propensity score matching, it

was not possible to completely eliminate the effect of subjective judgement on the determination of the therapeutic method.

In conclusion, our results suggest that surgical start times are correlated with surgical outcomes. Patients who underwent afternoon surgery had a greater incidence of intra-operative complications compared with those who underwent morning surgery. Our data will be helpful in ensuring the safest possible surgeries for patients with CRC.

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Compliance with ethical standards

Disclosures Drs. Y Ishiyama, F Ishida, S Ooae, Y Takano, J Seki, S Shimada, K Nakahara, C Maeda, Y Enami, N Sawada, E Hidaka, and S Kudo have no conflicts of interest or financial ties to disclose.

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