Effect of preoperative asymptomatic renal dysfunction on the clinical course after colectomy for colon cancer

Shinsaku Obara[1], Fumikazu Koyama[1,2], Hiroyuki Kuge[1], Takayuki Nakamoto[1,2], Naoya Ikeda[1], Yosuke Iwasa[1], Takeshi Takei[1], Tomomi Sadamitsu[1], Kosuke Fujimoto[1], Suzuka Harada[1], Masayuki Sho[1]

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[1]Department of Surgery, Nara Medical University, Nara, Japan

[2]Division of Endoscopy, Nara Medical University Hospital, Nara, Japan

Correspondence to: Masayuki Sho

Department of Surgery, Nara Medical University

840 Shijo-cho, Kashihara, Nara 634-8522, Japan

E-mail: m-sho@naramed-u.ac.jp

Telephone: +81-744-29-8863, Fax: +81-744-24-6866

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Abstract

Purpose: To evaluate the effect of mild renal dysfunction on the clinical course after colectomy in patients with colon cancer.

Methods: The subjects of this retrospective study were 263 patients who underwent surgical resection for colon cancer at our hospital between 2011 and 2015. Renal function was assessed based on preoperative estimated glomerular filtration rate (eGFR) values. Patients were divided into groups based on their eGFR value of 55 ml/min/1.73 m^2. The Mann-Whitney U test, chi-square or Fisher exact test, and log-rank test were used in the data analysis.

Results: There were 59 patients (22.4%) in the low eGFR group and 204 patients in the normal eGFR group. There were differences between the groups in age, comorbidities, and the levels of hemoglobin, albumin, and serum creatinine. The overall postoperative complication rate, frequency of severe complications, and length of stay were significantly higher in the low eGFR group than in the normal eGFR group. Multivariate analysis revealed that low eGFR was the only independent risk factor for severe complications (Clavien–Dindo classification III/IV). There were no differences in survival between the groups.

Conclusion: Preoperative asymptomatic renal dysfunction may be correlated with the

development of postoperative complications and a possible significant risk factor for severe complications after colon cancer surgery

Introduction

Colorectal cancer is the fourth-leading cause of cancer-related death, accounting for about 550,000–700,000 people deaths annually worldwide [1, 2]. The number of patients with colorectal cancer who require surgical treatment is increasing; accompanied by advances in surgical techniques and perioperative multidisciplinary treatment and the prevalence of bowel screening programs [3, 4]. Despite these advances, the postoperative morbidity rate of colorectal cancer is still high, ranging from 17.1% to 51.1% [4-6]. Although surgery for colon cancer seems to be less invasive and safer than surgery for rectal cancer, the rate of postoperative complications is still reported as up to approximately 30% [7-12]. Studies on colon cancer surgery have focused on the differences in safety and results between laparoscopic surgery and open surgery [7, 8, 10, 11]. However, studies on factors involved in postoperative complications are relatively limited. Renal failure requiring chronic hemodialysis is associated with metabolic and coagulopathic disorders, and is perceived as a risk factor for postoperative complications [13]. In cardiac and vascular surgery, preoperative renal dysfunction is one of the risk factors for postoperative morbidities [14-16]. Sirany et al. [17] and Drolet et al. [18] reported that chronic dialysis patients undergoing colorectal surgery had an increased risk of postoperative morbidity and mortality. Although severe renal failure is commonly recognized as a risk factor for

postoperative complications, the association between preoperative mild renal disorders and abdominal surgical outcomes is not fully understood. We reported previously on the correlation between preoperative asymptomatic renal dysfunction and postoperative complications after pancreatectomy [19] and esophagectomy [20]. Nagai et al. found that preoperative mild renal dysfunction was correlated with severe postoperative complications and grade B/C pancreatic fistula after pancreatoduodenectomy, classified as mild renal dysfunction according to an estimated glomerular filtration rate (eGFR) value of less than 55 ml/min/1.73 m^2 [19]. Kirihataya et al. also reported that the frequency of severe complications, such as respiratory events after esophagectomy, was significantly higher in patients with than in those without mild renal dysfunction, as defined by the eGFR value [20]. Taken together, mild renal dysfunction may be an important risk factor for abdominal surgery; however, to the best of our knowledge, no studies have reported on the correlation of mild renal dysfunction with postoperative complications of colon cancer. Therefore, we conducted this retrospective study to clarify the short-term and long-term postoperative outcomes after colectomy in colon cancer patients with asymptomatic renal disorder.

Methods

Study design and patients

From a total 269 patients who underwent surgical resection for colon cancer between 2011 and 2015 at Nara Medical University Hospital, 6 who were on maintenance hemodialysis were excluded from this study. The remaining 263 patients (136 men and 127 women; mean age, 69.6 years ± 11.2 standard deviation [SD]), were the subjects of this analysis.

Data and definitions

We reviewed the medical records of all patients comprehensively, to evaluate various clinicopathological factors including patient demographics, medical comorbidities, preoperative laboratory values, clinical and pathological tumor characteristics, and perioperative data. All patients had histologically proven colon cancer. Cardiovascular diseases included coronary artery disease, atrial fibrillation, valvular heart disease, and cerebral infarction. Respiratory diseases included chronic obstructive pulmonary disease, bronchial asthma, and interstitial pneumonia. Renal dysfunction was evaluated by calculating the eGFR based on the results of laboratory examination during the patient's first visit to our department. The eGFR value was calculated using the following formula:

eGFR (ml/min/1.73 m^2) = 194 × serum creatinine$^{-1.094}$ × age$^{-0.287}$ (×0.739 for female patients) [21].

Outcome assessments

We evaluated the incidence of postoperative complications that occurred within 30 days after surgery. The severity of complications was categorized according to the Clavien–Dindo (CD) classification [22]. The most severe grade was used if a patient suffered several complications. We defined severe complication as a complication of grade III or greater. We also evaluated the overall survival (OS) rate as the postoperative long-term outcome. The day of last follow up was May 31, 2020.

Measurement of the cut-off estimated glomerular filtration rate value to predict postoperative complications

To configure the optimal cut-off value of the eGFR to predict postoperative complications, we measured various values of eGFR (35–65 ml/min/1.73 m^2) in relation to all complications and severe complications. Consequently, we defined 55 ml/min/1.73 m^2 as the cut-off eGFR value. The patients were then allocated to the low or normal eGFR group based on this eGFR value. There were 204 patients (77.6%) with an eGFR ≥55

ml/min/1.73 m^2 in the normal eGFR group, and 59 patients (22.4%) with an eGFR <55 ml/min/1.73 m^2 in the low eGFR group (Fig. 1).

Statistical analyses

The continuous variables are expressed as the mean ± SD and were analyzed using the Mann–Whitney U test. The categorical variables were analyzed using the chi-square or Fisher exact test, as appropriate. The logistic regression model was used for multivariate analysis. We evaluated OS from the day of surgery until death or the last follow up. The Kaplan–Meier method was used to depict the OS curve and the difference between the groups was analyzed using the log-rank test. The difference was considered significant at *P*-value <0.05 and confidence intervals (CIs) were calculated at the 95% level. All statistical analyses were performed using the SPSS software program, version 19.0 (IBM Corp., Armonk, NY, USA).

Ethics statements

This study was approved by the ethics committee of Nara Medical University (No. 2116-2) and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All patients gave their informed consent

for the use of their anonymized data via an opt-out method. Patients consent to participate was obtained through the opt-out method.

Results

Clinicopathological characteristics of the normal and low estimated glomerular filtration rate groups

The mean eGFR value in patients with postoperative complications was significantly lower than that in patients without complications (62.3 ± 21.5 versus 69.6 ± 18.7, P = 0.02), although the difference between the mean values was relatively small. In this study, we divided patients into the two groups using a cut-off value of 55 ml/min/1.73 m^2 and compared them in the following analyses. Table 1 summarizes the patient characteristics in each group. The mean age of patients in the normal eGFR group was 68 years and that in the low eGFR group was 77 years and this difference was significant ($P < 0.01$). The low eGFR group had predominantly more male patients, but without significance (P = 0.06). Patients in the low eGFR group had more preoperative comorbidities ($P < 0.01$), including hypertension (44% versus [vs.] 71%) and cardiovascular disease (17% vs. 37%), than the normal eGFR group. The hemoglobin (12.3 ± 2.1 vs. 11.2 ± 1.8) and albumin

(4.2 ± 0.45 vs. 4.0 ± 0.47) levels were significantly higher in the normal eGFR group than in the low eGFR group. On the other hand, there were no significant differences in tumor location, clinical and pathological tumor depth, lymph nodal status, or tumor stage according to the Union for International Cancer Control (UICC) tumor-node-metastasis (TNM) staging system between the groups. There was also no significant difference between the right-sided and left-sided tumors, when we defined right-sided colon cancer as any tumor located in the cecum, ascending colon, or transverse colon.

Operative characteristics

Table 2 compares the operative characteristics between the normal and low eGFR groups. Intraoperative blood loss was slightly higher in the normal eGFR group than in the low eGFR group ($P = 0.02$). We found no significant differences in operative time, surgical procedure, surgical approach, extent of lymphadenectomy, or tendency of emergency operations between the groups.

Postoperative outcomes

Postoperative complications developed in 52 patients (19.8%; Table 3). There were significantly more patients with postoperative complications in the low eGFR group than

in the normal eGFR group ($P = 0.048$). However, there were no significant differences between the groups in any complication including ileus, anastomotic leakage, surgical site infection, and sepsis. We also analyzed the severity of postoperative complications according to the CD classification, and found that the low eGFR group had significantly more severe complications than the normal eGFR group (1% vs. 10%, $P < 0.01$). Severe complications were noted in three patients from the normal eGFR group (deep SSI, ileus, and anastomotic leakage in one each) and in six patients from the low eGFR group (ileus in three, leakage in one, anastomotic hemorrhage in one, and acute respiratory failure in one). No specific trend in postoperative complications was identified. The postoperative length of stay was also significantly longer for the low eGFR group than for the normal eGFR group (9.7 ± 4.5 vs. 12.0 ± 10.8, $P < 0.01$).

Analysis of risk factors for severe complications

Univariate analysis identified preoperative hemoglobin and low eGFR as significant risk factors for postoperative severe complications (Table 4). Clinical ≥T3 cancer seemed to be correlated with severe complications, although the difference was not significant ($P = 0.07$). Multivariate analysis of the three factors revealed a low eGFR to be the only predictor significantly correlated with postoperative severe complications (odds ratio 0.20,

95% CI 0.05–0.9, $P = 0.03$).

Long-term outcomes

Finally, we evaluated the impact of the eGFR value on long-term outcomes. No significant difference was observed in the OS rate between the groups (Fig. 2). Furthermore, when patients were divided according to the pathological stage of the UICC, the OS rate did not differ significantly at any stage between the normal and low eGFR groups.

Discussion

Preoperative renal insufficiency is associated with higher postoperative mortality and morbidity after cardiac, general, and other types of surgery [14-16, 23, 24]. Some studies have found that severe renal failure requiring dialysis is associated with poor surgical outcomes of abdominal surgery [25-27]. There are also published data describing the correlation between short-term outcomes after colorectal surgery for both benign and malignant diseases and severe preoperative renal failure [17, 18, 26, 28]. Hu et al. reported that dialysis status contributed significantly to higher rates of postoperative morbidity,

length of hospital stay, and 30-day mortality after colorectal cancer surgery [28]. Several other studies have also shown that a lower preoperative eGFR value was associated with unfavorable postoperative outcomes of gastrointestinal surgery [29-31]. Prowle et al. reported that the postoperative mortality increased steeply for patients with moderate to severe renal insufficiency [29]. However, the effect of mild renal dysfunction on outcomes of colorectal surgery has not been evaluated.

In this study, we tried to reveal the importance of asymptomatic renal dysfunction in the surgical treatment of colon cancer. We found that a preoperative eGFR <55 ml/min/1.73 m^2 was significantly correlated with overall postoperative complications in patients with colon cancer. Moreover, although surgery for colon cancer was thought to have few serious postoperative complications, the low eGFR group had a 10 times (10%) higher incidence of severe complications of CD III/IV than the normal eGFR group (1%). In the low eGFR group, three patients suffered postoperative ileus categorized as a severe complication. To prevent such complications in patients with a low eGFR, the use of the enhanced recovery after surgery protocol or adhesion barrier during surgery may be helpful. Interestingly, on investigating the long-term outcome of colon cancer surgery, we did not find a significant difference in the OS rate between the low and normal eGFR groups. These results suggest that surgical treatment is appropriate from the viewpoint of

cancer treatment, even though patients with mild renal dysfunction have a significantly higher risk of postoperative complications. We also analyzed the impact of mild renal dysfunction on surgery for rectal cancer and found that the postoperative complication rate after rectal cancer surgery did not differ significantly between the low and normal eGFR groups (data not shown). In the surgical treatment of rectal cancer, various factors, such as surgical procedures, neoadjuvant therapy, distance from the anal verge, presence or absence of stoma creation, and lateral lymph node dissection, may contribute to postoperative complications. In contrast, the surgical procedure for colon cancer is relatively generalized, and few factors would have had a significant effect on the postoperative complications, which seems to highlight the importance of mild asymptomatic renal dysfunction. Several mechanisms may be involved in the association of asymptomatic renal dysfunction with increased postoperative morbidity after colon cancer surgery. First, the tissue fragility of patients with renal dysfunction might have increased the risk of postoperative complications. There were some significant differences in patient characteristics including age, hypertension, cardiovascular disease, and hemoglobin and serum albumin levels between the low and normal eGFR groups. On the other hand, there were no significant differences between the groups in tumor status, such as the tumor location, clinical and pathological tumor depth, lymph node metastasis,

or stage according to the UICC TNM staging system. Multivariate analysis indicated that mild asymptomatic renal dysfunction was the only factor associated with postoperative severe complications, although no idividual comorbidity or laboratory finding was a significant risk factor for postoperative complications. The difference in the patient backgrounds may imply the frailty of patients with mild renal dysfunction resulting in a higher incidence of severe postoperative complications. Second, the perioperative infusion volume might have been involved. To prevent renal insufficiency, the infusion volume may be increased in patients with a mildly elevated serum creatinine level. However, it is unlikely since there was no significant correlation between the perioperative infusion volume and postoperative complications in this study (data not shown). Third, a subclinical metabolic disorder may have triggered postoperative complications, Mild asymptomatic renal dysfunction may induce subclinical metabolic acidosis. Raphael reported that subclinical metabolic acidosis may cause acid-mediated organ injury [32]. This mechanism may be involved in the increased risk of postoperative complications. Several fundamental mechanisms might have been complexly involved in the development of postoperative complications.

There were several limitations to this study reaching a definitive conclusion. First, it was a retrospective study performed at a single center. Second, the sample size

was relatively small. Third, it was unclear whether the cut-off eGFR value was appropriate. To identify the cut-off value of the eGFR more precisely, a larger validation study is needed. Further studies are also needed to clarify the underlying mechanisms and develop a novel treatment strategy for high-risk patients.

In conclusion, to our knowledge, this study is the first to show that colon cancer patients with mild asymptomatic renal dysfunction have a significantly higher risk of suffering postoperative complications than patients with a normal eGFR. Although no impact on long-term outcomes was identified, careful perioperative management and appropriate informed consent from patients with mild renal dysfunction are recommended.

Conflict of Interest Statement

We have no conflicts of interest to declare with respect to the research, authorship, and publication of this article.

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