Comparison of surgical outcomes between end-to-side and side-to-side anastomosis after laparoscopic right hemicolectomy: a prospective randomized controlled trial

Version No: 1.0

Principal Investigator Affiliation: Bundang Seoul National University Hospital

Principal Investigator Name: Sung-Bum Kang

Study Overview

Study Title	Comparison of surgical outcomes between end-to-side and side-to- side anastomosis after laparoscopic right hemicolectomy: a prospective randomized controlled trial
Principal Investigator	Professor Sung-Bum Kang, Department of Surgery, Bundang Seoul National University Hospital
Funding Institution	Bundang Seoul National University Hospital (In-House Research Project: 14-2016-016)

Study Objective	There is ongoing debate regarding the relationship between anastomotic techniques and surgical outcomes (such as recovery period and complications). To date, no prospective randomized clinical study has been reported comparing postoperative outcomes between end-to-side and side-to-side anastomosis following right hemicolectomy. This study aims to establish a standard anastomotic method after right hemicolectomy.
Study Design	a single center prospective randomized controlled trial
Study Duration	IRB Approval Date – June 30, 2018
Study Subjects	Patients scheduled for laparoscopic right hemicolectomy for right-sided colon cancer at Bundang Seoul National University Hospital.
Number of Study Subjects	130 patients (65 in the end-to-side anastomosis group, 65 in the side-to-side anastomosis group).
Vulnerable Study Subjects	Not applicable.
Investigational Drug/Medical Device	Not applicable.
Dosage and Administration	Not applicable.
Study Method	After random allocation of the anastomotic technique during surgery, a comparative analysis will be conducted between the two groups on cumulative recovery rate, length of hospital stay, complications, failure rate of the early recovery program, and readmission rate within one month after surgery.
Inclusion Criteria	• Patients scheduled for laparoscopic right hemicolectomy for right-sided colon cancer • Patients who will undergo an early recovery program after surgery
Exclusion Criteria	• Cases where laparoscopic surgery is not feasible due to a history of abdominal surgery or the severity of the disease • Individuals who do not consent to the study
Efficacy Assessment	• **Primary Outcome Variable:** 7-day cumulative recovery rate • **Secondary Outcome Variables:** Length of hospital stay, complications, failure rate of the early recovery program, and readmission rate within one month after surgery
Safety Assessment	All adverse events occurring in both groups (end-to-side anastomosis group and side-to-side anastomosis group) will be investigated, and an assessment will be made to determine which group experiences a higher occurrence.
Tests/Visit Schedule	Not applicable.
Statistical Analysis	The statistical analysis will be conducted using SPSS. A p-value of ≤ 0.05 will be considered statistically significant. **Continuous variables:** Student's t-test, Mann-Whitney U test **Binary variables:** χ^2-test, Fisher's exact test

Expected Benefits and Anticipated Outcomes	• This study may help establish a standardized anastomotic technique following right hemicolectomy. • It can provide scientific evidence for the optimal anastomotic method after colectomy, which may also be applicable to other gastrointestinal resections. • This research can serve as a foundation for expanding beyond a single-center study to a multi-center study.

Research Protocol

1. Study title: Comparison of surgical outcomes between end-to-side and side-to-side anastomosis after laparoscopic right hemicolectomy: a prospective randomized controlled trial

2. Name and Address of the Research Institution

1) **Name of Research Institution:** Bundang Seoul National University Hospital
2) **Address:** 82, Gumi-ro 173beon-gil, Bundang-gu, Seongnam-si, Gyeonggi-do, South Korea

3. Name and Title of Principal Investigator and Co-Investigators

1) **Principal Investigator:** Sung-Bum Kang, Professor, Department of Surgery, Bundang Seoul National University Hospital.

2) Co-Investigators:

- **Duck Woo Kim**, Associate Professor,
  Department of Surgery, Bundang Seoul National University Hospital
- **Heung Kwon Oh**, Associate Professor,
  Department of Surgery, Bundang Seoul National University Hospital
- **Il Tae Son**, Clinical Fellow,
  Department of Surgery, Bundang Seoul National University Hospital
- **Myung Jo Kim**, Clinical Fellow,
  Department of Surgery, Bundang Seoul National University Hospital
- **Jin Ah Kim**, Researcher,
  Department of Surgery, Bundang Seoul National University Hospital
- **Sang Ah Lee**, Researcher,
  Department of Surgery, Bundang Seoul National University Hospital

3) Research Coordinator: Sung Il Kang, Clinical Fellow,
Department of Surgery, Bundang Seoul National University Hospital.

4. Name and Address of the Research Sponsor: Not applicable.

5. Name and Address of the Funding Institution:

1) **Name of the Funding Institution:** Bundang Seoul National University Hospital
(In-House Independent Research Project: 14-2016-016)
2) **Address:** 82, Gumi-ro 173beon-gil, Bundang-gu, Seongnam-si, Gyeonggi-do, South Korea.

6. Expected Study Duration
: IRB Approval Date – June 30, 2018

7. Target Disease of the Study
: Right colon cancer

8. Background and purpose of study

1) Background

Since the development of surgical staplers, stapled anastomosis has largely replaced hand-sewn anastomosis in bowel anastomosis (1-3). Consequently, circular staplers have become the standard technique for colorectal anastomosis (4), particularly in minimally invasive procedures such as laparoscopic surgery, where they have become an essential technique.

However, no prospective comparative study has been conducted to determine whether end-to-side anastomosis or side-to-side anastomosis using a stapler is superior following right hemicolectomy. Only two retrospective studies have compared these two techniques. In the study by Puleo et al. (5), the incidence of anastomotic leakage was lower in the end-to-side anastomosis group compared to the side-to-side anastomosis group. In contrast, Liu et al. (6) found no significant differences between the two groups.

The authors previously reported that, when an early recovery program was applied after laparoscopic right hemicolectomy for right-sided colon cancer, the end-to-side anastomosis group had a higher cumulative recovery rate on postoperative day 7 (71.7% vs. 93.0%, p = 0.019), a shorter length of hospital stay (7 vs. 6 days, p = 0.003), and a lower complication rate (26.1% vs. 4.6%, p = 0.008) compared to the side-to-side anastomosis group (7). Another study reported that side-to-side anastomosis was a major factor contributing to early recovery program failure in patients, including those with not only right-sided colon cancer but also left-sided and sigmoid colon cancer (8).

2) Hypothesis and purpose

Currently, there is no established standard anastomotic technique for laparoscopic right hemicolectomy. End-to-side anastomosis is considered anatomically ideal, and it is hypothesized that it may result in superior short-term outcomes. This study aims to demonstrate the superiority of end-to-side anastomosis through a prospective randomized comparative study between end-to-side and side-to-side anastomosis.

9. Investigational Drug and Medical Device Code Name (or Generic Name of Active Ingredient), Quantity of Active Ingredient, Dosage Form (Including Comparator)

: Not applicable.

10. Selection Criteria, Exclusion Criteria, Target Sample Size, and Rationale for Sample Size Calculation

1) Selection Criteria:

Subjects must meet all of the following conditions:

① Patients with right-sided colon cancer

Right-sided colon cancer is defined as tumors located from the cecum to the hepatic flexure.

The histological type is limited to adenocarcinoma.

② Patients aged between 18 and 80 years
③ Patients with adequate bone marrow function:
Hemoglobin ≥ 10 g/dL (in cases of simple iron deficiency anemia, correction is required)
White blood cell count ≥ 4,000/mm^3
Platelet count ≥ 100,000/mm^3
④ Patients with adequate renal function (Creatinine ≤ 1.5 mg/dL)
⑤ Patients without significant functional impairment of the heart, lungs, or other major organs
⑥ Patients who have signed the written informed consent form

2) Exclusion Criteria
Patients who meet any of the following conditions will be excluded from this clinical trial:
① **Patients with distant metastasis or local invasion to the small intestine, ureter, or other adjacent structures requiring combined resection**
② **Patients in whom laparoscopic surgery is not feasible due to a history of prior abdominal surgery or the severity of the disease**
③ **Patients requiring emergency surgery due to bowel obstruction or peritonitis**
④ **Patients taking other oral medications for bowel movement disorders, such as chronic constipation, before surgery**
⑤ **Patients with severe cardiopulmonary disease, mental illness, or other comorbidities that prevent the application of the early recovery program**
⑥ **Patients who do not consent to the study or do not sign the informed consent form**
⑦ **Patients deemed ineligible for clinical trial participation based on the physician's judgment**

3) Target Sample Size and Rationale for Sample Size Calculation
This study aims to evaluate the superiority of end-to-side anastomosis over side-to-side anastomosis in terms of short-term outcomes. The sample size was calculated based on previous studies (7,9).
Allocation ratio: 1:1
Type I error (α): 5%
Power: 80%
Expected difference in 7-day cumulative recovery rate: 20% (End-to-side: 90% vs. Side-to-side: 70%)
Expected dropout rate: 10%
The calculated sample size is as follows:

◆ **Target number of participants**: **130**
End-to-side anastomosis group: 65 participants
Side-to-side anastomosis group: 65 participants
(*The sample size will be further reviewed and adjusted upon consultation with the Clinical Research Institute at Seoul National University.*)

◆ Randomization
The **allocation ratio** between groups will be **1:1**.
The anastomosis method will be determined preoperatively using a **random table or computer-generated randomization program**.
Group allocation will be revealed **in the operating room just before anastomosis**.
(*The randomization process will be conducted in consultation with the Clinical Research Institute at Seoul National University.*)

4) Recruitment Plan
There will be **no public recruitment announcement** for participant enrollment. Instead, patients admitted for **laparoscopic right hemicolectomy** for right-sided colon cancer will be provided with detailed information about the study, including its objectives, safety, and potential risks. After obtaining written informed consent, eligible patients will be enrolled in the study.

11. Study methods

1) Detailed methods

(1) Design

: Prospective randomized clinical trial

(2) Classification of Patient Groups

① Patient group classification will be revealed just before surgery.
② Patients will be randomly assigned into two groups: the end-to-side anastomosis group and the side-to-side anastomosis group.
③ Except for the anastomotic method, all other procedures will be conducted identically in both groups.

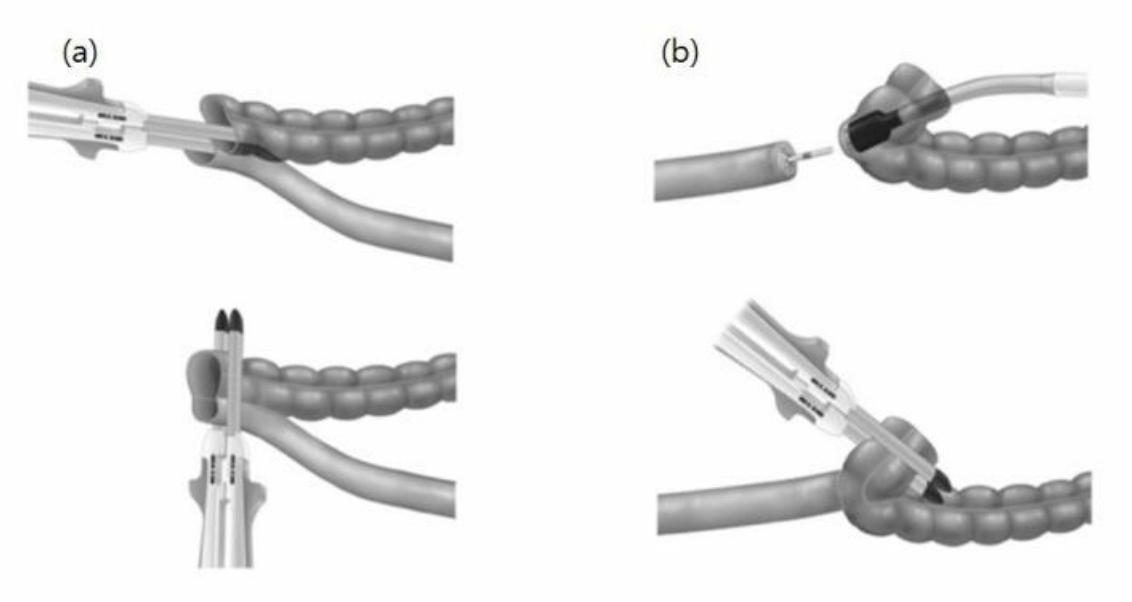

Figure 1. Schematic Diagram of Side-to-Side Anastomosis (a) and End-to-End Anastomosis (b)

(3) Postoperative Management

① All patients participating in the study will undergo the Enhanced Recovery Program (ERP) after surgery.
② The ERP protocol applied will be based on the protocol used in the researchers' previous studies.
③ If complications such as ileus or obstruction occur during the application of the ERP, the program will be immediately discontinued, and appropriate examinations and treatments will be administered at the physician's discretion. In such cases, it will be considered a failure of the ERP application.

Operative day	diet		exercis
Operative day	Sow of water	• After 4 hours of arrival in the hospital room from the operating room, initiate oral intake after confirmation by the attending medical staff. • Start with small sips to moisten the mouth and gradually increase the intake instead of consuming a large amount at once. • However, the total dietary intake should not exceed 1 liter per day. • If symptoms such as nausea, vomiting, or abdominal pain occur, discontinue oral intake and perform necessary examinations and treatments.	• Sit for a total of 1 hour per day. • Spend at least one hour per day out of bed. • Sitting can be divided into 4 sessions of 15 minutes each or 6 sessions of 10 minutes each. • Various options are allowed, such as sitting on the edge of the bed or sitting on the caregiver's bed.
Postoperative Day 1	Liquid diet (three times a day)	• Like water, liquid food should be consumed in small amounts initially and gradually increased rather than taken in large quantities at once. • There is no strict limitation on the amount, but if symptoms such as nausea, vomiting, or abdominal pain occur, discontinue intake and perform necessary examinations and treatments.	• Sit for a total of 3 hours per day. • Walk in the hospital corridor. If walking alone is difficult, assistance from a caregiver or the use of a walker is allowed.
Postoperative Day 2	Soft porridge (three times a day)	There is no strict limitation on the amount, but if symptoms such as nausea, vomiting, or abdominal pain occur, discontinue the diet and perform necessary examinations and treatments.	Walking in the hospital corridor: Walk back and forth along the corridor at least three times. If walking alone is difficult, assistance from a caregiver or the use of a walker is allowed.
After Postoperative Day 2	Soft porridge (three times a day)	There is no strict limitation on the amount, but if symptoms such as nausea, vomiting, or abdominal pain occur, discontinue the diet and perform necessary examinations and treatments.	Walking in the hospital corridor: Walk back and forth along the corridor at least three times. If walking alone is difficult, assistance from a caregiver or the use of a walker is allowed.

Table 1. Implementation of the Early Recovery Program

(4) Data Collection Items
① **Basic patient data** (age, sex, body mass index, medical history, ASA grade)
② **Preoperative staging** (CT, endoscopic findings)
③ **Intraoperative findings** (operative time, intraoperative blood loss)
④ **Postoperative course** (gas out time, length of hospital stay, recovery time, occurrence of complications)
⑤ **Histopathological results and staging**
⑥ **Readmission within one month after surgery and its reason**

2) Control Group Setting and Randomization Method
A comparison will be made between end-to-side anastomosis and side-to-side anastomosis.
Randomization will be conducted using the **SAS program**, managed by the **MRCC at Bundang Seoul National University Hospital**. A random number will be generated, assigned a serial number, and the anastomotic method will be delivered just before surgery to ensure random allocation.

3) Investigational Drug Administration/Usage, Method of Administration, Concomitant Therapy, and Justification for Comparator Use
Not applicable.

4) Observation Items, Clinical Examination Items, and Evaluation Methods for Study Outcomes
(1) Primary Endpoint: 7-Day Cumulative Recovery Rate
The **cumulative recovery rate** is defined as the percentage of patients who have reached **recovery time** within a specific postoperative period.
The definition of **recovery time** is based on previous studies by the investigators (7, 9) and is defined as the postoperative time at which **all** of the following conditions are met:
① **No issues for 24 hours after diet initiation** (at least one-third intake of liquid diet or higher).
② No additional analgesic administration after discontinuation of patient-controlled analgesia (PCA).
③ No major complications and stable afebrile condition (body temperature ≤ 37.2°C).
④ No issues with ambulation (ability to walk a distance of at least 600 meters).

(2) Secondary Endpoint

- **Length of hospital stay**
- **Complications**
- **Failure rate of the early recovery program**
- **Readmission rate within one month after surgery**

5) Criteria and Methods for Efficacy Evaluation

This study evaluates the superiority of end-to-side anastomosis over side-to-side anastomosis in terms of short-term outcomes. The sample size was calculated based on previous studies (7,9).

- **Allocation ratio:** 1:1
- **Type I error (α):** 5%
- **Power:** 80%
- **Expected difference in 7-day cumulative recovery rate:** 20% (End-to-side: 90% vs. Side-to-side: 70%)
- **Expected dropout rate:** 10%

The hypothesis to be tested is that the cumulative recovery rate in the end-to-side anastomosis group is 20% higher than in the side-to-side anastomosis group.

6) Differences from Existing Treatments and Studies

Both end-to-side and side-to-side anastomosis are standard anastomotic techniques commonly used in clinical practice, meaning that this study does not involve a new or experimental treatment. However, research specifically comparing anastomotic techniques in right-sided colon cancer is limited, with most existing studies being retrospective cohort studies. Thus, this study will be the first prospective, randomized controlled trial investigating anastomotic methods in right-sided colon cancer.

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7) Benefits and Risks for Study Participants

Since this study compares two existing standard anastomotic techniques, there are minimal risks or additional benefits associated with participation. Furthermore, the scientific and medical knowledge gained from this research is expected to far outweigh any potential risks or adverse effects experienced by study participants.

8) Discontinuation and Withdrawal Criteria

① Conversion to open surgery during the procedure due to safety concerns that make continued laparoscopic surgery unsafe for the patient.
② Participants who initially consented to the study but later decide to withdraw their consent.

9) Criteria, Methods, and Reporting for Adverse Events and Safety Evaluation

① This study compares two standard and well-established anastomotic techniques that are already considered safe and routinely used in clinical practice, even for patients who are not part of the study. Therefore, the likelihood of adverse events resulting directly from participation in this study is expected to be minimal.

② Even if a patient experiences postoperative side effects or complications, these are not caused by participation in the study but are general complications that can occur after laparoscopic right hemicolectomy. The presence or absence of such complications is also one of the comparison/evaluation criteria in this study.

10) Data Safety Monitoring Plan (DSMB)

(1) Monitoring Supervisor

- **Sung-Bum Kang (Principal Investigator, Professor of Surgery, Bundang Seoul National University Hospital)**

(2) Monitoring Frequency

- **Monitoring will be conducted when the 40th and 100th participants are enrolled.**

(3) Monitoring Method

- **Under the supervision of the monitoring supervisor, monitoring personnel will review essential documents and cross-check medical records for one participant.**

(4) Handling of Findings During Monitoring

- **The monitoring supervisor will determine the type and severity of findings in the monitoring report and may request reporting to the Institutional Review Board (IRB), implementation of corrective actions, and measures to prevent recurrence.**

(5) Reporting Procedures to the Institutional Review Board (IRB)

A. The monitoring report must be submitted to the IRB as an "Other Report" by the principal investigator.

B. Deadline for IRB reporting of findings identified during monitoring:

- Adverse Drug/Medical Device Reaction Reports (Fatal/Life-Threatening Cases):
  - **Initial report within 7 days + Follow-up report within 8 days**
- Adverse Drug/Medical Device Reaction Reports (Non-Fatal/Non-Life-Threatening Cases):
  - **Other cases (hospitalization or prolonged hospitalization, persistent or significant disability, congenital anomalies, significant medical events, etc.) must be reported within 15 days.**
- Safety Information Report: Once every 6 months
- Unexpected Problem Report: Within 15 days
- Major Noncompliance Report: Within 15 days
- Minor Noncompliance Report: Once every 6 months

(6) Review of Key Efficacy Evaluation Variables for Decisions on Study Continuation, Modification, or Termination

A. No interim analysis will be conducted for efficacy evaluation.

B. Safety review will be conducted as follows to determine study modification or termination:

- If a serious and unexpected adverse event occurs:
  - **(A) The principal investigator will review the event and decide on study modification or termination.**
  - **(B) If the IRB review results in a decision to modify or terminate the study, the research team will comply with the IRB's directive.**
- Safety review will be conducted once every 6 months:
  - **(A) The principal investigator will review all adverse events that occurred in the past 6 months and determine whether study modification or termination is necessary.**

    (B) **The findings reviewed in section (A) will be reported as an "Other Report" to the respective Institutional Review Board (IRB) of each institution.**

11) Data Analysis and Statistical Methods

- Statistical analysis will be conducted using SPSS or STATA. A p-value of ≤ 0.05 will be considered statistically significant.
  - **Continuous variables:** Student's t-test, Mann-Whitney U test
  - **Binary variables:** χ^2-test, Fisher's exact test
- If advanced statistical analysis techniques are required, consultation with the Medical Research Institute will be sought for expert statistical guidance and analysis.

12) Study Schedule

Contents	Duration											
	2	4	6	8	10	12	14	16	18	20	22	24
IRB Review	■	■										
Selection of Study Participants and Obtaining/Registration of Informed Consent		■	■	■	■	■	■	■				
Data collection		■	■	■	■	■	■	■				
Statistical analysis									■	■		
Final Report										■	■	
Final Research Paper											■	■

12. Measures for the Protection of Study Participants' Safety

1) Basic Measures to Ensure Ethical Conduct of the Study

- **The study will comply with the Declaration of Helsinki (2013 revision) and ICH-GCP guidelines.**
- **The study will be conducted only after obtaining IRB approval.**

2) Informed Consent Process for Study Participants

① Researchers responsible for explaining the study and obtaining consent: A physician among the research team.

② Individuals providing consent: Study participants.

③ Waiting period between study explanation and consent acquisition: 20 minutes.

④ Methods to minimize coercion or undue influence:
a. The researcher (usually the attending physician) will explain the study to the participant.
b. The research coordinator will provide additional explanations in a separate space.
c. The researcher will confirm if the participant has any additional questions before obtaining consent.

⑤ Language used by the researcher during the study explanation and consent process: Korean.

⑥ Language understood by the study participants or their legal representatives: Korean.

⑦ Information and consent form provided to the study participants or their legal representatives: Attached as a separate document.

3) Compensation Plan for Study Participants

- **This study does not involve new treatments or drugs but rather a comparison of already validated and standardized surgical techniques, minimizing any potential harm to participants.**
- **In the event of any harm resulting from the study, compensation will be provided in accordance with the Clinical Trial Compensation Guidelines.**

4) Measures for Protecting Study Participants' Personal Information

① Files containing patients' medical record numbers and pathology numbers will be stored separately under the responsibility of the principal investigator.
② Computer files will be password-protected and stored in a secured, locked research facility.
③ According to Article 15 of the Enforcement Regulations of the Bioethics and Safety Act, research-related records must be retained for three years after study completion. After this period, documents will be disposed of in accordance with Article 16 of the Enforcement Decree of the Personal Information Protection Act.

5) Additional Protection Measures for Vulnerable Study Participants

- **No vulnerable participants will be included in the study. (Not applicable.)**

13. Storage and Disposal of Human-Derived Materials

- **Not applicable.**

14. References

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6) Liu, Z., et al., Ileocolonic anastomosis after right hemicolectomy for colon cancer: functional end-to-end or end-to-side? World J Surg Oncol, 2014. 12: p. 306.
7) Lee, K.H., et al., Comparison of anastomotic configuration after laparoscopic right hemicolectomy under enhanced recovery program: side-to-side versus end-to-side anastomosis. Surg Endosc, 2015. Doi10.1007/s00464-015-4302
8) Oh HK, Ihn MH, Son IT et al. Factors associated with failure of enhanced recovery programs after laparoscopic colon cancer surgery: a single-center retrospective study Doi 10.1007/s00464-015-4420-6
9) Lee TG, Kang SB, Kim DW et al. Comparison of Early Mobilization and Diet Rehabilitation Program With Conventional Care After Laparoscopic Colon Surgery: A Prospective Randomized Controlled Trial. Dis Colon Rectum 2011 54(1): p21-8