THE SPARROW STUDY

Prospective, Multicentric Observational Cohort Study

Surgical Outcomes in SPlenic Flexure CAnceRs:

A CompaRison of Segmental Hemicolectomy vs. Extended HemicolectOmy, and KnoWledge Assessment

Study Protocol Version #6

02/01/2025

Partners

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ABSTRACT

Background

Colonic cancers arising at the splenic flexure are rare, representing less than 10% of all surgically treated colorectal cancers. The optimal surgical approach for these cancers remains a subject of debate, with extended colectomy and segmental colectomy being the two primary options; however, no prospective multicentre study has yet been conducted.

Methods

This prospective, multicenter observational cohort study aims to compare the surgical outcomes of extended colectomy and segmental colectomy in patients with splenic flexure cancers. A total of 140 patients (70 per group) will be recruited from centers. Primary outcomes will include short-term perioperative metrics such as ileus, anastomotic leakage, wound infection, postoperative complications, recovery to a regular diet, and the time to first flatus. Secondary outcomes will encompass a broader range of indicators, including lymph node harvest, R0 resection, postoperative mortality, 3-year overall survival, 3-year disease-free survival, operation time, blood loss, hospital stay, and reoperation.

Discussion

To our knowledge, this prospective multicenter observational study will be the first to prospectively and objectively assess these two surgical approaches in this context. By evaluating short-term perioperative outcomes, complication incidences, and early postoperative recovery, this research aims to provide valuable evidence to guide surgical decision-making. The findings may contribute to standardizing treatment protocols and improving patient outcomes for this rare subset of colorectal cancers.

Trial Registration: ClinicalTrials.gov ID: [To be completed upon registration]

Keywords: Splenic flexure cancer, extended colectomy, segmental colectomy, left colectomy, extended right colectomy, short-term outcomes, postoperative recovery, colorectal surgery.

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BACKGROUND INFORMATION & RATIONALE

Colonic cancers arising at the splenic flexure are relatively rare, accounting only less than 10% of all surgically treated colorectal cancers.[1,2] These tumors, located at the junction of the left and right colonic vasculature, often present challenges in determining the optimal surgical approach due to their unique anatomical positioning.[3] The surgical options generally considered are left colectomy and extended right colectomy.[4–6]

The choice between these two surgical approaches can significantly impact various factors, including operative time, intraoperative blood loss, lymph node yield, and postoperative complications. Moreover, the extent of resection may influence early recovery metrics such as the return of bowel function, length of hospital stay, and quality of life in the immediate postoperative period.[7–9] The splenic flexure's anatomical complexity, characterized by variable blood supply and lymphatic drainage, further complicates the decision-making process.[3]

While extended right colectomy often allows for a tension-free ileocolic anastomosis and is associated with a well-perfused anastomosis, left colectomy may involve high tie of the inferior mesenteric artery and ligation of the left branch of the middle colic artery, or selective ligation of the left colic artery with a transverse-sigmoid anastomosis. Extended left colectomies sometimes necessitate right colonic transposition to achieve a tension-free anastomosis. Despite potential benefits, the literature lacks consensus and evidence on which surgical approach provides superior short-term outcomes and better early postoperative recovery..[8,10] To bridge the existing knowledge gap, this study aims to compare the outcomes of left colectomy versus extended right colectomy for treating splenic flexure cancers. We will evaluate both short-term perioperative outcomes and long-term results to provide evidence-based guidance for optimizing surgical decision-making for these challenging tumors.

AUDIT STANDARTS

Pre-operative	
1. Pre-operative Bowel Preparation	Appropriate pre-operative bowel preparation should be performed.
2. Localization of Splenic Flexure	Accurate macroscopic localization of the splenic flexure must be corroborated by colonoscopy reports or imaging studies (CT scan) or intraoperative exploration.
3. Antibiotic Use	Appropriate antibiotic standards should be followed for all patients to minimize the risk of postoperative infections and promote optimal patient outcomes.
4. Fluid Balance	Appropriate fluid balance standards should be established and consistently followed for all patients to minimize the risk of complications.

Post-operative	
1. Critical Care Access	There must be availability of critical care beds, including both level 2 and level 3, along with on-site renal support.

METHODS

1. Summary

This prospective, multicentric observational cohort study aims to compare outcomes between segmental colectomy and extended colectomy for splenic flexure cancers based on the surgeon's preference and standard practice at each participating center. The study will enroll patients from multiple tertiary centers. Commencing in *****, it will span approximately 5 years, including 24 months for patient enrollment and 5 years for follow-up, to evaluate both short-term and long-term surgical outcomes.

2. Study Aims:

2.1. Primary endpoint:

To investigate short-term perioperative outcomes, with a focus on postoperative ileus. Additional outcomes will include anastomotic leakage, wound infection, and total postoperative complications.

2.2. Secondary endpoint:

To evaluate long-term and procedural outcomes, such as lymph node harvest, R0 resection status, postoperative mortality, 3-year overall survival, and 3-year disease-free survival. Further, the study will assess operation time, intraoperative blood loss, hospital stay duration, and the incidence of reoperation.

3. Project Timeline:

The study will commence on ***** 1, 2025, with a planned enrollment period of 24 months. Each patient will be followed for 36 months to assess both short-term and long-term outcomes.

Dates	Description
1st ***** 2025	Online launch of **SPARROW** protocol
1st ***** 2025	Virtual conference for **SPARROW** study launch
1st ***** 2025 – 30st ***** 2025	Data collection period 1 (+ 30-day follow-up) (+ 6-month follow-up) (+ one-year follow-up) (+ three-year follow-up) (+ five-year follow-up)
1st ***** 2025 – 30st ***** 2025	Data collection period 2 (+ 30-day follow-up) (+ 6-month follow-up) (+ one-year follow-up) (+ three-year follow-up) (+ five-year follow-up)
1st ***** 2025 – 30st ***** 2025	Data collection period 3 (+ 30-day follow-up) (+ 6-month follow-up) (+ one-year follow-up) (+ three-year follow-up) (+ five-year follow-up)

4. Ethics Approval:

The study protocol will be submitted to the Ethics Committee of Koc University for approval. Written informed consent will be obtained from all participants for the acquisition and use of anonymised clinical data prior to enrollment, and all investigators will conduct this study in accordance with the tenets of the Declaration of Helsinki.

5. Centre Eligibility:

The SPARROW Study is open to any tertiary colorectal cancer centers in Turkey and Europe that routinely performs segmental colectomy and extended colectomy for splenic flexure cancers.

- All participating centers must register with the SPARROW study according to local regulations. In Turkey, the study must be reviewed and approved by the relevant ethics committees, while in Europe, centers should follow their respective national guidelines for research approval.
- Individual study investigators are responsible for obtaining the necessary institutional and ethical approvals before initiating data collection. This may include registering the study as an audit or service evaluation where applicable.
- Evidence of successful registration and approval must be submitted to the SPARROW study management team prior to the start of data collection. Centers will not be permitted to upload patient data onto the study platform without this documentation.

Participating surgeons: The participating surgeons should meet the following qualifications:

- Experience with Splenic Flexure Cancers: Surgeons must have completed at least 20 cases of surgery for colorectal cancer cases per year.
- Training and Expertise: Surgeons must have completed a general surgery training program.

6. Patient Eligibility:

a. Inclusion Criteria

Consecutive adult patients undergoing elective resection of splenic flexure cancer will be included in the study.

- Adult patients (≥18 years old)
- Histologically confirmed adenocarcinoma of the splenic flexure
- Candidates for curative surgical resection
- Able to provide informed consent

b. Exclusion Criteria

- Preoperative imaging examination results showing distant metastasis
- Previous colorectal or colonic surgery, including history of colectomy
- Simultaneous or simultaneous multiple primary colorectal cancer
- Need for an emergency operation because of conditions such as perforation or malignant colonic obstruction
- Significant comorbidities precluding surgery
- History of any other malignant tumour in the recent 5 years, except for cervical carcinoma in situ that has been cured, basal cell carcinoma, or squamous cell carcinoma of the skin
- Colonic stent insertion or primary diverting colostomy before elective surgery
- History of Ulcerative Colitis or Crohn's disease
- Hereditary colon cancer
- Pregnancy or breastfeeding in women
- Refusal to provide informed consent

7. Data Governance:

a. Sample size considerations

On the basis of previous data comparing extended right colectomy, and left colectomy, the incidence of postoperative ileus was observed to be 32.7% (36/110) in the extended right colectomy group and 10.9% (12/110) in the left colectomy group. Two-by-two comparisons yielded a p-value of 0.014 with an odds ratio of 3.97 (95% CI: 1.93–8.16). Using the categorical variable of postoperative ileus from this retrospective research, we calculated our sample size for the prospective study using the Cramer's V method. The Cramer's V value was determined to be 0.25. This was assessed using an exact p-value of 0.05 and a power of 0.80. Based on these parameters, the total sample size needed for the study is 126 patients, which would be 63 patients per group. Thus, the total sample size is set to 140 patients (70 per group), considering a maximum dropout rate of about 10% for this clinical study.

b. Data Recording

Data will be collected prospectively and recorded in a standardized case report form. Only the principal investigator, co-investigators, and assigned research personnel will access to the information. Each hospital has access to their own dataset. The study patients' medical record number will identify patients who are included in the datasheet.

Included centers must ensure that data collection is at least 90% complete. Centers with more than 10% missing data, when considering all data points, will be excluded from the final analysis and removed from authorship. There is no minimum patient number required per center, provided that all eligible patients treated during the study period are included.

c. Statistical Analysis

Statistical analysis will be performed using R version 4.2.3. Descriptive statistics will summarize patient characteristics. The study will be conducted in two phases: short-term and long-term outcomes. For the short-term phase, primary outcomes such as postoperative complications and immediate surgical outcomes will be compared between

left colectomy and extended right colectomy groups using chi-square or Fisher's exact tests for categorical variables, and t-tests or Mann-Whitney U tests for continuous variables, as appropriate. Multivariable logistic or linear regression models will be used to adjust for potential confounders. These short-term results will be published as an interim analysis. For the long-term phase, survival outcomes will be analyzed using Kaplan-Meier curves, log-rank tests, and Cox proportional hazards models once sufficient follow-up data is available.

Subgroup analyses will explore treatment effects across different patient characteristics in both phases. Missing data will be reported and addressed using multiple imputation if necessary. Sensitivity analyses will assess the robustness of findings. All tests will be two-sided with a significance level of $p \leq 0.05$, and adjustments for multiple comparisons will be made where appropriate.

8. Variable of Interests:

a. Demographic, Patient, and Preoperative Variables

- Age at diagnosis
- Gender / ASA (American Society of Anesthesiologists) Score
- Diagnosis date
- BMI (kg/m²) / Weight loss > 10% / Smoking
- Previous abdominal surgery
- Preoperative treatment / Preoperative imaging (US / BT / MRI / Colonoscopy)
- Tumor size / Tumor position and location
- Distance to anal verge
- Bowel preparation
- Hemoglobin (g/dL) / Albumin (g/dL) / CEA (Carcinoembryonic Antigen) (ng/mL)
- Clinical TNM (Tumor, Node, Metastasis) Stage
- Adjuvant therapy / Neoadjuvant therapy
- Comorbidities: Myocardial Infraction (MI) / Congestive Heart Failure (CHF) / Peripheral Vascular Disease (PVD) / Cerebrovascular Accident (CVA) or Transient Ischaemic Attack (TIA) / Dementia / Chronic Obstructive Pulmonary Disease (COPD) / Connective Tissue Disease (CTD) / Peptic Ulcer Disease (PUD) / Hemiplegia / Leukaemia / Lymphoma / Human Immunodeficiency Virus (HIV) or Acquired Immunodeficiency Syndrome (AIDS) / Hypertension / Inflammatory Bowel Disease (IBD) / Diabetes Mellitus (Type 1 or Type 2)
- Solid Tumour. If yes: Localised / Metastatic
- Chronic Kidney Disease (CKD). If yes: Stage I / II / IIIa / IIIb / IV / V

b. Intraoperative Variables

- Surgical approach (open, laparoscopic, robotic, robotic converted to open, laparoscopic converted to open)
- Total operative time
- Estimated blood loss (EBL)
- Anastomosis type
- Conversion to open surgery
- Any complications (intraoperative)
- Type of procedure (Primary anastomosis, Two-step procedure via temporary ostomy)

c. Postoperative Variables

- Gastrointestinal Symptom Rating Scale
- First flatus
- Ileus
- Quality of life measurements (EORTC QLQ-C30)
- Return to regular diet / Return to normal activities
- Postoperative length of stay
- Readmissions within 30 days
- 30-day mortality
- Clavien-Dindo Score
- Need for a stoma
- Anastomotic leak
- Chest infection / Atrial fibrillation / Acute coronary syndrome / Heart failure / Acute renal failure
- Postoperative ileus
- Clostridium difficile colitis
- Wound infection
- Reoperation
- Follow-up (months)
- Recurrence
- Time from the date of surgery to the date of death (Overall Survival - OS)
- Time from the date of surgery to the date of recurrence or death from any cause (Recurrence-Free Survival - RFS)

Tumor Pathology:

- Histology / Grade
- Pathological TNM Stage
- Number of lymph nodes harvested / Number of positive lymph nodes
- Margins
- Specimen surface in cm^2 (range)
- Tumor size (largest dimension, cm)
- Microsatellite instability (MSI) / DNA mismatch repair (MMR)
- Lymphovascular invasion / Perineural invasion

9. Authorship:

Surgeons will bear overall responsibility for data collection. The minimum requirements for authorship include:

- Each surgeon must complete a minimum of 10 cases during the data collection period to qualify for authorship.
- Successful completion of data collection at a center that meets the criteria for inclusion within the SPARROW dataset is mandatory.
- The hospital lead surgeon from each center will be responsible for their own data collection.
- The hospital lead surgeon will also maintain communication with the SPARROW Steering Committee to ensure compliance with study protocols and timely reporting of progress.

Note: If a surgeon provides more than 20 cases during the data collection period, they have the right to include two names in the SPARROW study authorship.

APPENDIX A: STUDY DEFINITIONS

Splenic Flexura:

The splenic flexure is defined as the colonic segment extending from the distal one-third of the transverse colon to the proximal one-third of the descending colon, specifically 10 cm from either side, where the distal transverse colon turns toward the proximal descending colon. This definition is based on an International Expert Consensus using the Delphi Technique. In this study, the distal one-third of the transverse colon to the proximal one-third of the descending colon will be accepted as splenic flexure cancers. Accurate macroscopic localization of the splenic flexure is essential and must be corroborated by colonoscopy reports, imaging studies, or intraoperative exploration.

Surgical technique:

- **Segmental Colectomy:** Segmental colectomy (SC) involves the resection of the bowel between the left branch of the middle colic artery (MCA) and left colic artery (LCA).
- **Extended Colectomy:**

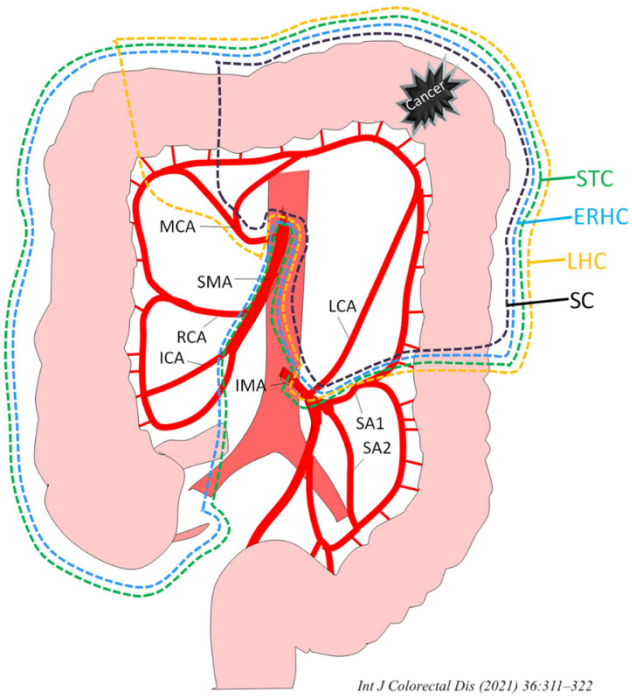
Extended colectomy includes extended right hemicolectomy, left hemicolectomy, and subtotal colectomy.

The definitions of these procedures are as follows:

⇒ **Extended right hemicolectomy**: Extended right hemicolectomy (ERHC) involves resection from the terminal ileum to the middle descending colon, ligation of the ileocecal artery (ICA), right colic artery (RCA), MCA and LCA.

⇒ **Left hemicolectomy:** Left hemicolectomy (LHC) involves resection of the last third of the transverse colon, descending and sigmoid colon down to the recto-sigmoid union, ligation of the left branch of the MCA and inferior mesenteric artery (IMA).

⇒ **Subtotal colectomy:** Subtotal colectomy (STC) resection of the right, transverse, descending and sigmoid colon down to the rectosigmoid union, ligation of ICA, RCA, MCA and IMA.



Note: The choice of laparoscopic or robotic surgical approach, as well as the type of anastomosis, may be determined based on the surgeon's experience and preference.

Definitions of Other Variables:

- **Prolonged postoperative Ileus:** Prolonged postoperative ileus was defined by the presence of at least two or more of the following symptoms on postoperative day 4: vomiting/nausea, inability to tolerate oral intake, abdominal distension, or radiological findings indicating ileus persisting for more than 24 hours.
- **Anastomotic Leak:** An anastomotic leak was defined as the presence of extraluminal contrast detected on radiological imaging or as an intraoperative finding. Only leaks that necessitated reoperation were included.
- **Postoperative Follow-Up:** Patients were scheduled for follow-up appointments over a 3-year period. The standard follow-up protocol included clinical examinations at 1, 6, 12 and 36 months postoperatively. Patients presenting with symptoms indicative of recurrence were investigated immediately. Patients lost to follow-up or discharged were tracked through passive follow-up methods.

- **Reoperation:** Reoperation was defined as any surgical intervention performed in the operating theatre under regional or general anesthesia following the primary surgery, either during the same hospitalization or within 30 days postoperatively.
- **Pathological Assessment**: The pathological report included an evaluation of the completeness of resection (R-stage), ensuring that at least 12 lymph nodes were harvested, and assessing proximal and distal margins. Tumor staging followed the 8th edition of the American Joint Committee on Cancer (AJCC) classification.
- **Recurrence:** Recurrence was defined as the presence of radiological or histological evidence indicating the return of the disease.
- **Mortality:** Postoperative mortality was defined as death occurring within 30 days after surgery.

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