MULTICENTER PROSPECTIVE STUDY PROTOCOL FOR VALIDATING SURGICAL QUALITY STANDARDS IN D3 LYMPHADENECTOMY FOR ONCOLOGICAL RIGHT HEMICOLECTOMY

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ABSTRACT

Introduction: D3 lymphadenectomy (D3L) for right hemicolectomy, proposed by Eastern guidelines, aims to improve oncological outcomes by extending resection to include lymphatic drainage zones beyond those addressed by complete mesocolic excision (CME). However, the absence of standardized anatomopathological quality parameters limits its validation. This multicenter study seeks to validate this criteria, including the "right mesocolic sail," to classify D3L specimens and evaluate its clinical and oncological implications.

Materials and Methods: This prospective, multicenter study involves 11 hospitals in Spain. Surgical specimens from right hemicolectomy with D3L will be analyzed for the presence of the "right mesocolic sail" and classified as complete or incomplete D3L. Standard CME criteria will also be applied. Patient data, surgical details, and oncological outcomes at 3 and 5 years will be collected. Statistical analysis will compare lymph node retrieval, recurrence rates, survival outcomes, and perioperative complications between groups.

Results: The study will validate the right mesocolic sail as a quality parameter for D3L. Preliminary data from prior phases confirm increased lymph node retrieval and the presence of positive nodes in D3L specimens. Additional analyses will determine the impact of D3L on recurrence rates, survival, and perioperative risks.

Discussion: This study aims to provide standardized anatomopathological criteria to evaluate D3L, facilitating comparative studies and addressing its controversial oncological benefits. If validated, the criteria could enhance surgical quality assessment and inform future guidelines.

Keywords

Colon neoplasm; D3 lymph node excision; Oncological outcomes; Pathology quality; Multicenter study

INTRODUCTION

Background & Rationale

As with total mesorectal excision (TME) and complete mesocolic excision (CME), anatomopathological parameters allow for the classification of a surgical specimen as satisfactory, partially satisfactory, or unsatisfactory mesorectum or mesocolon. D3 lymphadenectomy (D3L) should also have its own anatomopathological parameters.

The evolution of CME has followed a development similar to that of TME. First, the surgical technique was standardized based on embryological and anatomical concepts. Subsequently, the description of quality anatomopathological parameters allowed for the classification of specimens. This classification has enabled prospective comparative studies analyzing local recurrence rates and medium- and long-term survival percentages, demonstrating the benefits of the described technique (1).

Colon cancer shows a local recurrence rate of approximately 11%, as reported in the study published by *Green* in 2012 (CLASSIC trial) (2). Specifically, this series reports a 14,7% recurrence rate after right colon surgery compared to 5,2% in the left colon and sigmoid.

The CME technique for right hemicolectomy, proposed in 2008, is based on resection along the embryological planes between the mesocolon and the retroperitoneum, as well as high ligation of the tumor's nutrient vessels. *Hohenberger* reported a 5-year survival rate of 82,1% with conventional surgery, which increased to 89,1% with CME. Additionally, it reduced the 5-year local recurrence rate for stage III disease from 6,5% to 3,6% (3).

In 2008, *West & Quirke* published a retrospective study analyzing the relationship between survival and the quality of the mesocolic plane. This was based on the classification used in the CLASSIC trial (inspired by the classification for mesorectal quality evaluation in the MRC CR07 study), where specimens were classified based on mesocolon characteristics (4).

This study observed a 15% improvement in 5-year survival when comparing mesocolic and intramuscular planes. Other authors have utilized this classification to compare their results (5).

D3L in right hemicolectomy has been proposed by Eastern countries as an extended resection to the third lymphatic station to reduce local recurrence and improve survival. The Japanese Society for Cancer of the Colon and Rectum (JSCCR) in its 2019 guidelines (6), recommend D3L in all cases with positive lymphatic metastases (either preoperative or intraoperative suspicion). Preoperative suspicion is determined based on CT findings. However, preoperative CT demonstrates an accuracy of 60% for detecting lymph node infiltration (7). For cases without suspected nodal involvement, D3L is recommended from cT3 stage onwards. However, the JSCCR also recommends D3L for cT2 cases, as 10% of cT2 cases present nodal involvement. This is due to inaccuracies in assessing wall involvement, with CT overstaging 23,7% of cases and understaging 48,3%.

The technical difference between CME and D3L is not easy to understand, as both involve dissection along the embryological plane and high ligation of the primary vessels to achieve an extensive lymphadenectomy, including the main lymphatic station.

However, the difference is conceptual. The Eastern school argues that lymphatic drainage originates embryologically from the venous system. While CME focuses on high ligation of the arterial tumor-nutrient vessels, D3L also incorporates venous drainage zones into the surgical specimen. In fact, *Mike Maio* argues that venous vascularization is equally or more important than arterial vascularization in right hemicolectomy. D3L was defined based on anatomical findings by French surgeon *Gillot* (8,9).

In his work, *Gillot* emphasized the importance of the Henle's trunk area, formed by the confluence (with varying drainage patterns) of the superior right colic vein (SRCV), the right gastroepiploic vein (RGEV), and the inferior anterior pancreaticoduodenal vein (IPDV). This zone drains into the superior mesenteric vein (SMV) without accompanying arterial branches. *Gillot* highlighted its significance as the upper limit of what he termed the surgical trunk of the SMV. This trunk comprises the right ventrolateral area of the SMV, bordered cranially by the Henle's gastrocolic trunk (HGCT) and caudally by the ileocolic vein. Since the 1970s, the Eastern school proposed incorporating the lymphoadipose tissue from the HGCT and the surgical trunk into the surgical specimen. This latter zone was named Gillot's surgical trunk (GST) in his honor (8,9).

Some authors argue that not all HGCT tissue should be included in right colon cancer surgery due to the risk of SMV damage, which could lead to massive intraoperative bleeding. The SRCV has been suggested as the only vein in this area to be included in the D3L specimen (10).

Despite strong recommendations from the Japanese Society for extended lymphadenectomy, systematic reviews from European groups conclude that there is no evidence supporting D3L to the D3 territory described (11,12).

Given the surgical field manipulated during D3L, this technique may be associated with a higher number of intraoperative complications, such as retroperitoneal organ injury (e.g., duodenum and pancreas) or venous bleeding due to avulsion or tearing of the HGCT or SMV (13).

To date, no prospective comparative studies have demonstrated the benefits of this technique due to the lack of D3L surgical quality parameters that would allow for comparison.

The research group leading this multicenter study published in 2020 in the Q1 journal *Diseases of the Colon and Rectum* a set of proposed anatomopathological standards for surgical specimens to determine whether a proper D3L was performed (14).

The study consisted of two phases: anatomical-surgical and real cases.

1. Phase One: Potential D3L anatomopathological standards were established by studying surgical specimens from right hemicolectomies with D3L performed on human cadavers. The two quality parameters identified were the "right mesocolic sail" and the SRCV trunk.
2. Phase Two: These two parameters were confirmed to be useful for classifying surgical specimens as complete or incomplete D3L.

Validating these proposed parameters through a multicenter study is necessary before their widespread adoption.

Objectives

The main objective is to validate, through a multicenter study, the effectiveness of the new anatomopathological quality criteria for right hemicolectomy with D3 lymphadenectomy (D3L) in correctly classifying surgical specimens.

Secondary objectives are:

1. To evaluate the increase in the number of lymph nodes retrieved following D3L.
2. To demonstrate the presence of lymph nodes in the D3L area.
3. To assess whether performing right hemicolectomy with D3L increases the risk of perioperative complications.
4. To examine the potential oncological benefits of D3L (e.g., local recurrence, systemic recurrence, and three- and five-year survival).

The hypothesis entails that the presence of the "right mesocolic sail" in the surgical specimen can be considered an anatomopathological standard of a correctly performed D3L. Using this parameter and those described by *Quirke* for CME, specimens can be classified into the following groups:

- Non-CME and Non-D3L: Incorrect mesocolic plane and absence of the right mesocolic sail.
- CME: Correct mesocolic plane and absence of the right mesocolic sail (Figure 1).
- CME + D3L: Correct mesocolic plane and presence of the right mesocolic sail (Figure 2).

This classification could help resolve the question of whether D3 lymphadenectomy improves long-term oncological outcomes.

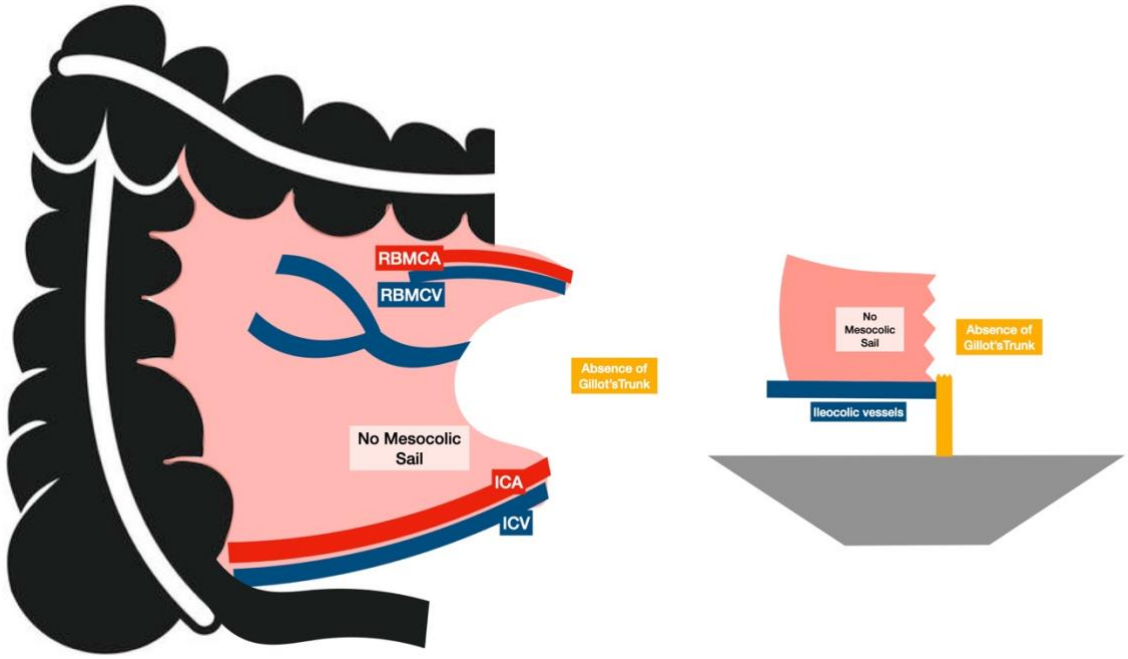


Figure 1 Complete Mesocolic Excision (CME): Correct mesocolic plane and absence of the right mesocolic sail. The absence of Gillot's trunk or the "mast" creates the rupture of the mesocolic sail landmark. RBMCV: Right branch of middle colic vein, RBMCA: Right branch of middle colic artery, ICA: ileocolic artery, ICV: Ileocolic vein.

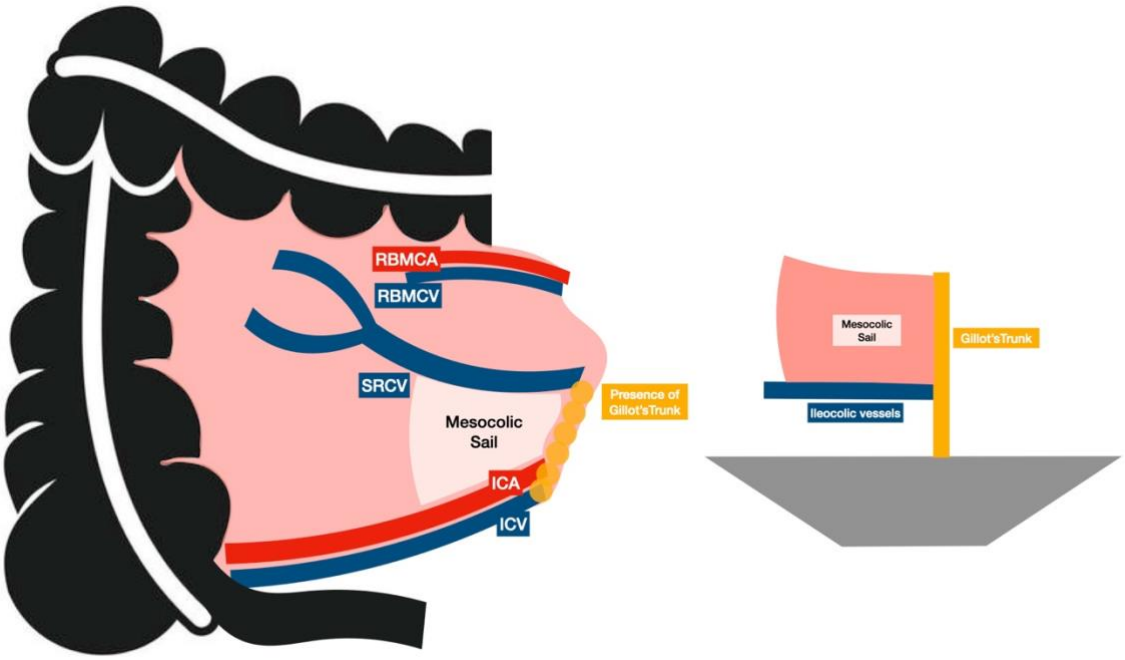


Figure 2 Complete Mesocolic Excision (CME) + D3 Lymphadenectomy (D3L): Correct mesocolic plane and presence of the right mesocolic sail. The presence of Gillot's trunk as the "mast" allows the mesocolic sail to be preserved. RBMCV: Right branch of middle colic vein, RBMCA: Right branch of middle colic artery, SRCV: Superior right colic vein, ICA: ileocolic artery, ICV: Ileocolic vein.

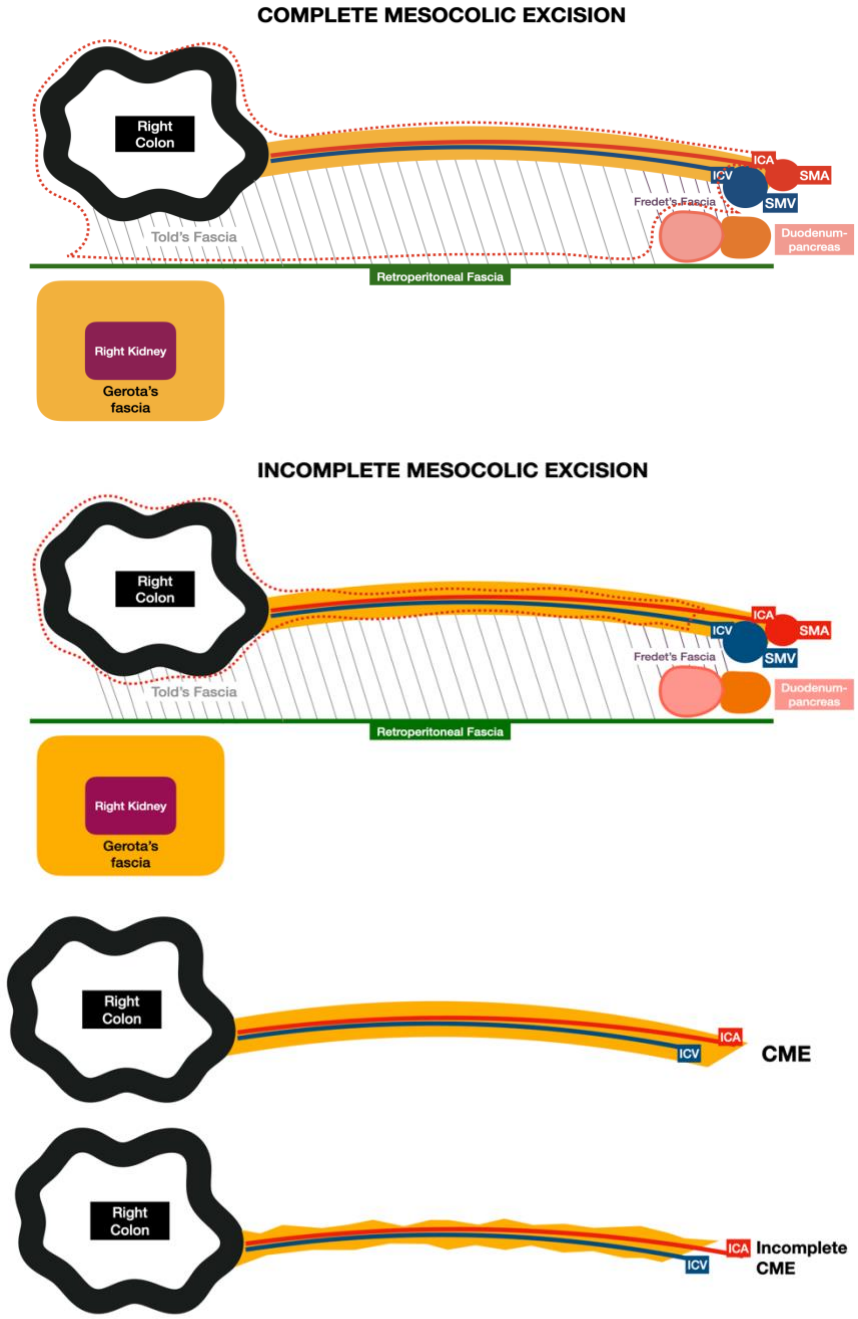


Figure 3 Complete Mesocolic Excision (CME) & Incomplete CME. Complete CME shows smooth mesocolon throughout dissection while incomplete CME shows a rough mesocolon surface. ICA: ileocolic artery, ICV: Ileocolic vein. SMA: Superior mesenteric artery, SMV: Superior mesenteric vein

Trial Design

Prospective, comparative multicenter study involving 11 different hospitals in Spain.

METHODS: Participants, interventions, and outcomes

Study Design

Prospective, comparative multicenter study.

A prospective anatomopathological study of all surgical specimens is going to be obtained following oncological resection for localized cancer in the cecum, ascending colon, or hepatic flexure.

Eligibility Criteria

The study includes consequent patients undergoing either elective or emergency surgery with a diagnosis of adenocarcinoma or adenoma with dysplasia located in the cecum, ascending colon, or hepatic flexure of the colon.

Exclusion criteria include patients under 18 years of age or lack of informed consent for inclusion in the study.

Surgical specimens will always be analyzed by the same pathologists at each center.

Interventions

D3L implies dissection of embryological plane of the right mesocolon (Toldt's and Fredet's fascia), high tie of ileocolic vessels and their origin at SMV and Superior mesenteric artery (SMA), high tie of right colic artery if present, dissection of the lymphoadipose tissue over SMV (Gillot's trunk), SRCV ligation as it enters into the Henle's trunk, high tie of right branch of middle colic vessels and hepatocolic, phrenocolic and parietocolic ligament division as described by Garcia-Granero et al in their D3L standardization proposal (15).

Pathological specimen analysis protocol is going to be described as follows:

Mesocolic Plane:

- Satisfactory (smooth surface)
- Unsatisfactory (irregular surface)

Retroperitoneal Resection Margin

Staining of the retroperitoneal area with Indian ink and evaluation of potential involvement (13):

- Clear: Tumor infiltration is more than 1 mm away from the ink.
- Involved: Tumor infiltration is less than 1 mm from the ink.

Specific Anatomopathological Protocol for D3L:

Before slicing each surgical specimen, a specific search will be conducted for the structures defined as D3 lymphadenectomy standards, specifically the "right mesocolic vein" or the right mesocolic sail. Based on the presence or absence of this anatomical structure, surgical specimens will be classified as:

- Complete D3 lymphadenectomy: Presence of the right mesocolic sail.

- Incomplete D3 lymphadenectomy: Absence of the right mesocolic sail.

The presence of the mesocolic sail will be considered confirmed if a "mast" is present in the surgical specimen. A mast is defined as the lymphatic fatty tissue within the mesocolic sail. The D3 lymphadenectomy area corresponds to the mast of the sail.

A specific analysis will be performed to evaluate the number of lymph nodes and the number of positive lymph nodes within the D3 lymphadenectomy area. The D3 lymphadenectomy area is equivalent to the mast of the sail.

Anatomopathological Classification of the Surgical Specimen:

- Non-CME and Non-D3L: Incorrect mesocolic plane and absence of the right mesocolic sail.
- CME: Correct mesocolic plane and absence of the right mesocolic sail.
- CME + D3L: Correct mesocolic plane and presence of the right mesocolic sail.

Outcomes

The primary outcome is validation of Anatomopathological Criteria for Quality Assessment: to validate, through a multicenter study, the effectiveness of new anatomopathological criteria for right hemicolectomy with D3 lymphadenectomy (D3L) in accurately classifying surgical specimens as complete or incomplete D3L.

Secondary Outcomes include:

1. Lymph Node Retrieval:
    - To evaluate the increase in the number of lymph nodes retrieved following D3L.
    - To confirm the presence of positive lymph nodes within the D3 lymphadenectomy area.
2. Perioperative Risk Assessment:
    - To assess whether performing right hemicolectomy with D3L increases perioperative complications.
3. Oncological Outcomes:
    - To examine the potential oncological benefits of D3L, including:
        - Local recurrence rates.
        - Systemic recurrence rates.
        - Three- and five-year survival rates.

These outcomes aim to establish whether the application of D3 lymphadenectomy improves oncological outcomes and ensures standardization in surgical specimen quality evaluation.

Project and participants timeline

Year 1:

- Training via digital meetings for surgeons and pathologists on the study of surgical specimens.
- Patient inclusion, data collection, and patient follow-up. Patient follow-up will be done using the American Society of Colorectal Surgeons (ASCRS) guidelines.

Year 2:

- Continued patient follow-up, clinical data collection, analysis of results, manuscript preparation, and scientific communications.

Year 3:

- Collection of oncological data and analysis of results.

Year 5:

- Collection of oncological data and analysis of results.

Sample Size

The study will be carried out in all cases that meet the inclusion and exclusion criteria established at the centers involved.

Recruitment

Patients eligible for the study will be identified and recruited from participating hospitals based on predefined inclusion and exclusion criteria. Recruitment will focus on individuals undergoing procedures relevant to the study objectives, ensuring alignment with eligibility standards.

All potential participants will receive comprehensive information about the study's purpose, procedures, potential risks, and benefits through detailed informed consent discussions. Recruitment efforts will prioritize voluntary participation, ensuring that patients have ample opportunity to ask questions and make informed decisions before enrollment.

The recruitment process will adhere to ethical guidelines, with continuous oversight to maintain transparency and participant safety throughout the study.

METHODS: Data collection, management and analysis

Data collection methods

A specific protocol for analyzing colon cancer specimens is going to be provided for each center.

Specific Pathological Protocol for Complete Mesocolic Excision (CME)

- Mesocolic plane:
    - Satisfactory (smooth surface)
    - Unsatisfactory (irregular surface)
- Retroperitoneal resection margin:
    - Staining with India ink to evaluate potential involvement:
        - Free: Tumor infiltration is more than 1 mm from the ink.
        - Involved: Tumor infiltration is less than 1 mm from the ink.

Specific Pathological Protocol for D3 Lymphadenectomy (D3L)

- Before dissecting each specimen, the structure defined as the standard for D3 lymphadenectomy—the "right mesocolic sail"—will be specifically sought. Based on the presence or absence of this anatomical structure, specimens are classified as:
    - Complete D3 Lymphadenectomy (presence of the right mesocolic sail)

    - Incomplete D3 Lymphadenectomy (absence of the right mesocolic sail)
- Right mesocolic sail:
    - Defined by the presence of a "mast" with lymphatic and fatty tissue.
    - The D3 lymphadenectomy area corresponds to the "mast" of the sail.
- The number and positivity of lymph nodes in the D3 lymphadenectomy area will be specifically analyzed.

Analyzed Variables

Preoperative Variables:

- Age and sex
- ASA classification:
    - ASA I: Healthy patient
    - ASA II: Mild systemic disease
    - ASA III: Severe systemic disease not life-threatening
    - ASA IV: Severe systemic disease that is a constant threat to life
- Surgical history (presence or absence of prior abdominal surgery)
- Distant metastases at intervention or postoperative admission
- Preoperative CT findings:
    - T classification
    - N classification
    - Peritumoral collection
    - Tumor perforation

Surgical Description:

- Information from the operative report, including type of surgery, approach, tumor location, and ligation of tumor-nutrient vessels.
- Surgery types:
    - Right hemicolectomy: Ligation of ileocolic vessels and the right branch of the middle colic vessels (for cecum and ascending colon tumors).
    - Extended right hemicolectomy: Ligation of ileocolic and middle colic vessels (for hepatic flexure tumors).
    - Right hemicolectomy with D3 lymphadenectomy: Includes ligation of nutrient vessels, removal of lymphatic tissue over the superior mesenteric vein, and ligation of the superior right colic vein.

Intraoperative Variables:

- Urgent vs. scheduled surgery
- Tumor location: cecum, ascending colon, or hepatic flexure
- Type of surgery (as defined above)
- Whether D3 lymphadenectomy was performed: Yes/No

- Surgery duration (in minutes)
- Surgeon specialization:
    - Colorectal specialist (unit member or fellowship trainee)
    - Non-specialist
- Laparoscopic, robotic or open surgery and any conversion to open surgery
- Intraoperative findings of carcinomatosis (confirmed by pathology).

Postoperative variables

Multiple critical variables occurring during the hospital stay are going to be analyzed, based on daily clinical progress, vital signs, and the results of laboratory and imaging tests. These variables include:

- Bleeding: Defined as the need for transfusion within the first 24 hours postoperatively due to hypovolemic shock or surgical reintervention for hemoperitoneum.
- Reintervention: Any secondary surgical procedure required postoperatively.
- Anastomotic Dehiscence:
    - *Minor clinical leak*: Radiologically detected leaks (perianastomotic collection with pneumoperitoneum bubbles) that do not require aggressive measures (reintervention and/or percutaneous drainage) but may prolong hospital stay (Clavien-Dindo grades I-II) (13).
    - *Major clinical leak*: Leaks requiring reintervention or percutaneous drainage (Clavien-Dindo grades III-IV-V) (13).
- Paralytic Ileus: Defined as an absence of intestinal transit for 6 days or more.
- Occurrence of Medical Complications: Considered significant when consultation with another specialist was required for treatment.
- Wound Infection: Diagnosed clinically by the presence of inflammatory signs at the surgical wound site or pathological exudate.
- Total Length of Hospital Stay: Recorded in days.
- Clavien-Dindo Classification: Used to grade complications (I, II, III, IV, V).

Pathological Study:

- Macroscopic protocol:
    - Distance of the tumor to proximal and distal margins (<1 cm compromises surgical margin)
    - Mesocolic plane (satisfactory or unsatisfactory)
    - Presence of right mesocolic sail (yes/no)
- Microscopic protocol:
    - Histological type (e.g., adenocarcinoma, adenoma with low-/high-grade dysplasia)
    - Differentiation grade (poorly, moderately, or well differentiated)
    - Total and positive lymph nodes
    - TNM staging (pT, pN, pM)
    - Mucin-producing tumors (≥50% of extracellular mucin)

- Vascular, lymphatic, or perineural invasion
- Tumor perforation (yes/no)
- Mesocolic plane (satisfactory/unsatisfactory)
- D3 lymphadenectomy (complete/incomplete)
- D3 area lymph nodes: total number and positive nodes
- Retroperitoneal resection margin:
  - Free: Tumor infiltration >1 mm from ink
  - Involved: Tumor infiltration ≤1 mm from ink
- Circumferential resection margin (for T4b tumors):
  - Free: Tumor infiltration >1 mm
  - Involved: Tumor infiltration ≤1 mm

For retroperitoneal infiltration zones, the retroperitoneal margin is analyzed instead of the circumferential margin.

Oncological Variables Analyzed at 3 and 5 Years:

- Locoregional recurrence
- Distant recurrence
- Carcinomatosis
- Disease-free survival
- Overall survival
- Mortality due to oncological progression

To differentiate locoregional recurrence from carcinomatosis:

- Carcinomatosis: Defined as tumor implants in at least two different areas of the abdominal cavity, confirmed by pathological diagnosis showing the presence of tumor cells.

Data Management

The information is stored in cloud servers owned by Oracle. The information is encrypted in Database (DB) so any direct access to the DB is useless unless the private key is known. No data that could be used to locate the patient such as name, surname, ID number, etc., is requested. The only data that could be used is the Clinical history ID, which is trimmed, so that the user who reports data can locate the correspondence in his/her hospital, i.e. he/she must have the real data written down in some place controlled only by them (such as the hospital management program itself) to be able to locate that patient.

In the event of access to the application by someone unauthorized but who has obtained a username and password with access to read patients from their own and other hospitals, the information available does not serve to "de-anonymize" the data. The accesses to the application, writings, readings, etc. are registered by the application so that any access without express authorization can be located.

Statistical methods

Qualitative variables are going to be expressed as sample size and percentage, while quantitative variables are going to be reported as median and range. For non-parametric univariate analysis, continuous variables were compared using the Kruskal-Wallis test, and categorical variables were analyzed with Fisher's Exact test. Statistical significance was determined at a p-value of < 0.05.

METHODS: Monitoring

Data Monitoring

Data collection and storage will be securely managed using Oracle cloud servers, with encryption in place to prevent unauthorized access. Each patient's data will be de-identified, and Clinical History IDs will be trimmed to enhance security. Additionally, access logs will monitor all database activities, including writing and reading, to detect and prevent unauthorized use.

Significant complications or protocol violations will be promptly reported to the ethics committee and documented in regular study reports.

Harms

Potential harms from the study may include:

- Perioperative Complications:
    - Bleeding: Intraoperative venous bleeding or hemoperitoneum requiring transfusion or surgical reintervention.
    - Retroperitoneal Organ Injury: Damage to structures such as the duodenum, pancreas, or Henle's gastrocolic trunk and its tributaries.
    - Anastomotic Dehiscence: Ranging from minor clinical leaks (radiological detection) to major leaks requiring reintervention or percutaneous drainage.
    - Paralytic Ileus: Defined as absence of intestinal transit for six or more days.
    - Wound Infection: Diagnosed clinically by inflammatory signs or exudate at the surgical site.
    - General Medical Complications: Includes any adverse event requiring specialist consultation for treatment.
- Postoperative Risks:
    - Prolonged hospital stay.
    - Increased morbidity due to perioperative events (e.g., transfusions, reoperations).

Ethics approval and informed consent procedures ensure that patients are aware of these risks before participating in the study.

Auditing

Internal audits will be conducted regularly to ensure strict compliance with the study protocol. These audits will include verification of the informed consent processes, assessment of the accuracy and completeness of data entry within the centralized cloud-based system, and periodic checks to confirm adherence to surgical and pathological standard operating procedures.

External monitoring will involve auditing of participating hospitals by researchers from the main center. This process will verify proper patient recruitment and adherence to eligibility criteria, as well as consistency in the application of pathological evaluation protocols across all sites. Comprehensive auditing records will document any deviations from the established protocol and recommend appropriate corrective actions as needed.

ETHICS AND DISSEMINATION

Research ethics approval

This study has been approved by the research ethics committee. Each participating center is required to obtain approval from their hospital's ethics committee.

Consent

Patients will be informed of the possibility of participation in the study and will need to sign an informed consent form (Human Ethics and Consent to Participate) before enrollment. Patients will be able to withdraw consent at any time without affecting their medical care they will receive. Moreover, the study will be performed in accordance with the Declaration of Helsinki. The main investigators will be responsible for adequate inclusion of patients and data recording.
All patients receive a patient information sheet for research projects and signed a written informed consent.

Availability of data

The datasets generated and analyzed in the present study are available from the corresponding author upon reasonable request.

Declaration of interests

The authors declare that they have no conflicts of interest.

Dissemination policy

Dissemination of the results in the National Congress of Surgery (Asociación Española de Cirujanos), National Congress of Coloproctology (Asociación Española de Coloproctología – AECP), International Congress of European and American Coloproctology and European Congress of Endoscopic Surgery. Articles of the study will be sent to high-impact factor journals, most likely Q1 Journal Citation Reports (JCR) journals.

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