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Protocol

A Comparison between Open and Minimally Invasive Right Hemicolectomies in Patients with Locally Advanced UICC Stage III Colon Cancer: A Protocol for a Systematic Review and an Individual Patient Data Meta-Analysis

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Abstract: Despite the development of new technologies and multimodal therapies, improving the prognosis of patients with UICC stage III right colon adenocarcinoma remains challenging. Several randomized controlled trials have shown the oncological non-inferiority of minimally invasive surgery compared to open surgery for colon cancer patients. However, for UICC stage III patients, carrying the highest risk for local recurrence and the worst survival, the evidence remains inconclusive. The aim of this systematic review and individual patient data meta-analysis is to improve the scarce evidence regarding minimally invasive surgery for this subgroup of patients. Data from adult patients with pathologically UICC stage III right adenocarcinoma of the colon will be included. The intervention to be assessed is the minimally invasive right hemicolectomy in comparison with the open procedure. The primary outcome will be the 5-year overall survival. Secondary outcomes will include further long-term outcomes, such as disease-free survival, short term, and histological outcomes. Only randomized controlled trials and quasi-randomized controlled clinical trials will be included. The literature search will be conducted in the following databases: PubMed, CINAHL, Cochrane Trials, ClinicalTrials.gov, and Web of Science. The review will be performed using the Cochrane methodology including GRADE tools. The findings of this meta-analysis will be important for choosing optimal treatment pathways and tailoring of surgical therapy in patients with locally advanced UICC stage III right colon cancer.

Keywords: colon cancer; right hemicolectomy; minimally invasive surgery; open surgery; individual patient data review

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1. Introduction

Surgery is considered the most important therapeutic measure in the curative treatment of right colon cancer [1,2]. The aim of this systematic review and individual patient data meta-analysis project (IPD) is to compare oncological outcomes of minimally invasive and open surgery. The study will focus on right-sided colon cancer patient data, as carcinomas in this location are associated with a poorer outcome than left-sided colon cancers [3].

There has been little development in the surgical techniques used for right colon cancers over the last decade, leading to a scarcity of evidence, and consequently, in potentially sub-optimal surgery [4,5]. There have been several studies, including randomized controlled trials, comparing minimally invasive and open approaches to colon cancer [6–9]. The oncological non-inferiority of minimally invasive procedures has been shown in nearly all of these trials. In addition, improved short term outcomes after minimally invasive surgery have been shown [10]. More recent meta-analyses suggest that hand-assisted laparoscopic right hemicolectomy might be an effective alternative to open right hemicolectomy for right-sided colon cancer, with benefits such as reduced hospital stay and similar mortality and oncological success [11,12].

The optimal therapy for the subgroup of patients with UICC stage III colon cancer, however, is still under debate. In this stage, locoregional lymph node metastases are present in the mesocolon. These metastases have a high potential to lead to recurrences if they remain in situ after surgery. Therefore, differences in the various surgical approaches should be demonstrated specifically in this patient group. Consequently, a meta-analysis should be particularly sensitive to clinically relevant differences.

It is still unclear whether this subgroup of UICC stage III patients benefits from either the minimally invasive or the open approach. Lacy et al., who published a randomized controlled trial about open versus minimally invasive procedures for colon cancer in 2002, noted a significant difference in the frequency of recurrence, overall survival, and cancer related survival for the laparoscopic surgery group for the UICC stage III subgroup [13]. A subsequent randomized controlled trial, published by the COST study group in 2007, was not able to confirm these results and the authors suspected that the previously described differences were due to an underpowered subgroup analysis [14]. On the other hand, long-term results of the CLASICC trial recognized a trend favoring open surgery for UICC stage III patients [15]. Additionally, a retrospective population-based analysis by Benz et al. observed better long-term survival for UICC III right colon cancer patients who were operated on using a minimally invasive approach compared to open surgery [16]. The prognosis for UICC stage III patients remains disappointing [17]. Thus, it is particularly important to investigate the most effective surgical therapy to provide the best possible prognosis for this high-risk cohort.

In conclusion, the current evidence is too scarce to derive definite recommendations for either minimally invasive or open surgery for UICC III right colon cancer. The ARI-COS systematic review and individual patient data meta-analysis project aims to fill this specific gap in evidence by gathering the individual outcome data for UICC III patients from all relevant randomized controlled trials comparing open and minimal-invasive right hemicolectomies.

2. Materials and Methods

2.1. Registration

This protocol has been registered within the International Prospective Register of Systematic Reviews (PROSPERO registration number: CRD42021176789) and was drawn up according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols' (PRISMA-P) 2015 statement [18]. The PRISMA-P 2025 checklist is shown in Table 1.

The "Cochrane Handbook for Systematic Reviews of Intervention" is used as a guideline for methodological implementation of the protocol and review [19].

Table 1. PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist.

Section and Topic	Item No	Checklist Item	
Title: Identification	1a	Identify the report as a protocol of a systematic review	see: Title
Title: Update	1b	If the protocol is for an update of a previous systematic review, identify as such	not applicable
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	see: Methods
Authors: Contact	3a	Provide name, institutional affiliation, email address of all protocol authors; provide physical mailing address of corresponding author	see: Affiliations
Authors: Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	see: Author contributions
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	not applicable
Support: Source	5a	Indicate sources of financial or other support for the review	see: Funding
Support: Sponsor	5b	Provide name of the review funder and/or sponsor	see: Funding
Support: Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	see: Funding
Rationale	6	Describe the rationale for the review in the context of what is already known	see: Introduction
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	see: Introduction
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame), and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility of the review	see: Methods

Table 1. *Cont.*

Section and Topic	Item No	Checklist Item	
Informatio n sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	see: Methods
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	see: Methods
Study records: Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	see: Methods
Study records: Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	see: Methods
Study records: Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, performed independently, in duplicate) and any processes used to obtain and confirm data from investigators	see: Methods
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), and any preplanned data assumptions and simplifications	see: Methods
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	see: Methods
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias in individual studies, including whether this will be carried out at the outcome or study level, or both; state how this information will be used in data synthesis	see: Methods
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	see: Methods
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	see: Methods

Table 1. *Cont.*

Section and Topic	Item No	Checklist Item	
	15c	Describe any additional analyses proposed (such as sensitivity or subgroup analyses, meta-regression)	see: Methods
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	see: Methods
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	see: Methods
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	see: Methods

2.2. Inclusion and Exclusion Criteria for Studies

To ensure the high reliability of the results, only randomized controlled trials and quasi-randomized controlled clinical trials will be considered. Quasi-randomized studies are defined as studies with inadequate methods of sequence generation, including allocation according to postal code, date of birth, case number, or date of presentation [20]. All types of retrospective study designs, such as retrospective case-control studies or case series or case reports, will be excluded. In addition, studies using data from registries in a retrospective manner will be excluded. Studies with less than 10 eligible patients will be excluded from this study for practical reasons.

2.3. Inclusion and Exclusion Criteria for Participants

Only patients with histologically confirmed UICC stage III adenocarcinoma of the right colon are eligible for this study. This includes tumors located in the right colic flexure and transverse colon, that can be operated on with an extended right hemicolectomy. UICC stage III is defined as a lymph node-positive tumor (T1-T4, N1-N2) without distant metastases. Patients without histologically confirmed lymph node infiltration (UICC I or II) or metastases in organs other than local lymph nodes (UICC IV) are excluded. Likewise, patients with other types of colon cancer such as endocrine tumors or familial tumor syndromes, as well as data from patients younger than 18 years, will be excluded.

2.4. Index Intervention

The intervention to be investigated is the minimally invasive right hemicolectomy. This term includes laparoscopic surgery, as well as laparoscopic-assisted, hand-assisted, robotic, single- and multi-incision procedures. No restrictions will be made regarding intra- or extracorporeal anastomosis, learning curve of the surgeon and standardization. Extended right hemicolectomy will be included as a subgroup.

2.5. Comparators

The minimally invasive procedures listed above will be compared to open right hemicolectomy.

2.6. Outcomes and Prioritization

The primary outcome is 5-year overall survival. Secondary outcomes are 5-year incidence of recurrence, 3-year overall survival, 5-year cancer related death, and 5-year disease-free survival. As short-term outcomes, postoperative 30-day mortality, postoper-

ative morbidity (Clavien–Dindo Score), duration of surgery, and length of hospital stay will be investigated. Histological parameters that will be recorded are resection status, number of harvested lymph nodes, and lymph node ratio. Furthermore, the learning curve, standardization of technique, and quality of life outcomes will be qualitatively assessed and discussed in relation to the primary and secondary outcomes of this analysis and of the primary studies.

2.7. Timing

Since the primary outcome of this study is the 5-year overall survival, inclusion requires a minimum follow-up period of 5 years for individual patient data. Therefore, we will consider all studies with published long-term oncological outcomes. Published early outcome data from ongoing studies, without publication of oncological long-term outcomes, will not be included.

2.8. Setting

There will be no restrictions regarding the setting of the studies (mono-centric and multi-centric studies; studies in hospitals of all healthcare levels).

2.9. Language

All articles found through the English literature search will be screened regardless of their original language. We will include articles reported in English or German language. Other possibly relevant articles reported in other languages will be provided as an appendix.

2.10. Search Methods for Identification of Studies

A computer-based literature search was performed using the following databases: the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Database of Systematic Reviews (CDSR) from The Cochrane Library, MEDLINE (1966 to present), CINAHL (1981 to present), and Web of Science (1945 to present). Moreover, the following online study registry of ongoing trials was searched: www.clinicaltrials.nci.nih.gov. No language restrictions were applied. Grey literature databases were not included in the formal search. The Cochrane Highly Sensitive Search Strategy for identifying clinical trials in MEDLINE, sensitivity-maximizing version, was employed with predefined search terms to identify all published studies on the topic, including clinical trials and meta-analyses. It was adapted for the other databases searched. Reference lists of retrieved articles were scanned for further eligible trials (backward search) and citations of identified trials were checked for inclusion (forward search). Furthermore, reference lists of articles and table of contents of relevant magazines were screened, to find additional relevant literature.

The PROSPERO register for meta-analysis and IPD was searched for similar projects.

The search was conducted in cooperation with a librarian and information specialist familiar with meta-analysis and lead by Cochrane Collaboration standards. The MEDLINE search strategy is displayed in Box 1.

2.11. Study Selection Process

The results of the systematic literature search will be transmitted into a shared EndNote library.

The reviewing process will be undertaken by two independent reviewers (JR, SB) according to the inclusion criteria listed above. In case of disagreement, a third person (FH) will be consulted. If necessary, study authors will be contacted to resolve uncertainty regarding eligibility of studies.

The studies will be screened for eligibility based on title and abstracts. For all reports judged to be eligible after abstract screening, or in case of uncertainty regarding the eligibility of a trial, a full-text review will be completed. All studies excluded after screening

of abstracts and full texts will be listed and reasons for exclusion will be reported. Neither of the two reviewers will be blinded to journal, study authors, and institution.

Box 1. Medline search strategy.

(Colo*[tiab] OR Cecal[tiab] OR Cecum[tiab] OR coecum[tiab]) AND ("Neoplasms"[Mesh] OR Neoplas*[tiab] OR Tumor*[tiab] OR Tumour*[tiab] OR Cancer*[tiab] OR Carcinoma*[tiab] OR malignancy[tiab] OR adenocarcinoma*[tiab] OR adenoma*[tiab]) AND ("Minimally Invasive Surgical Procedures"[Mesh] OR "Minimal Access"[tiab] OR "Minimal Invasive"[tiab] OR "Minimally Invasive"[tiab] OR "Minimal surg*"[tiab] OR Laparoscop*[tiab] OR "Da vinci"[tiab] OR "Davinci"[tiab] OR "Robotic Surgical Procedures"[Mesh] OR "Robotic Surg*"[tiab]) AND (Open[tiab]) AND (clinical trials as topic[mesh: noexp] OR randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR randomly[tiab] OR trial*[tiab] OR systematic review*[tiab] OR Study[tiab] OR studies[tiab])

2.12. Data Management and Collection Process

After the studies have been judged to be eligible and the corresponding authors have given their consent to participate, the individual patient data will be requested via a reply data form including pre-specified data items. A data use and sharing agreement between the authors of the original studies and the IPD research team will be provided, stating that only members of the research team will have access to the data and attempts at the re-identification of patients by the research team are prohibited. De-identification of patient data is required. Data will be collected and re-coded in a standardized form to facilitate the analysis. Only data relevant for either primary or secondary outcomes or baseline differences between intervention groups will be obtained. In case of missing data for primary or secondary outcomes, the review team will re-ensure with the original researchers that the missing data items do not exist.

To give the opportunity to confirm the accuracy of extracted data and information from the studies, the original researchers will receive a draft version of the review before publication.

2.13. Risk of Bias Assessment

Risk of bias assessment for the randomized controlled trials will be conducted using the Cochrane risk of bias 2.0 tool [20]. This tool works by signaling questions that allow to categorize studies as "low risk of bias", "some concerns", and "high risk of bias". Seven domains of risk of bias will be assessed for each study: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. For non-randomized (quasi-randomized) controlled clinical trials, the Cochrane ROBINS-1 tool [21] will be used. Both tools facilitate and standardize the process of risk of bias assessment. Authors will be contacted to resolve uncertainty if necessary. For the assessment, information about studies is retrieved from several publications of one study as well as conference papers, protocols, and international and national trial registries, e.g., clinicaltrials.gov. The risk of bias 2.0 and ROBINS-1 tools only refer to one outcome at once, so that this assessment will focus on the primary outcome of this study, which is the 5-year overall-survival and two more secondary outcomes (5-year disease-free survival and 30-day mortality). However, further information such as missing outcome data and selective reporting of outcome data will be collected for all included studies. All decisions will be reported and justified by explanations including quotes from the study reports. The risk of bias assessment will be conducted independently by two reviewers. In case of disagreement the third person (FH) will be consulted. The GRADE-method and tool [22] will be used to assess the confidence

in cumulative evidence of the study. The results of the assessment will be published with the review.

2.14. Data Items

A list of pre-specified data items for data to be retrieved from original researchers is shown in Table 2. Only data relevant for the outcomes listed above will be sought. The rationales for the outcomes were briefly described above.

Table 2. Pre-specified data items to be retrieved from original researchers.

- Age;
- Sex;
- ASA-Score I-VI;
- Body height, Body weight;
- Tumor location (coecum, ascending, hepatic flexure);
- Procedure (right hemicolectomy, extended right hemicolectomy);
- Minimally invasive (yes/no);
- Conversion to open surgery (yes/no/n.a.);
- Open operation (yes/no);
- Minimally invasive procedure (single-incision, multi-incision, robotic, laparoscopic-assisted, hand-assisted, n.a.);
- Adjuvant chemotherapy (yes/no);
- Death during study follow-up (yes/no);
- Date of primary surgery;
- Date of death;
- Date of last follow up;
- Local tumor recurrence during follow-up (yes/no);
- Distant metastasis during study follow-up (yes/no);
- Date of diagnosis of recurrence;
- Cause of death colon cancer related (yes/no);
- Clavien-Dindo Classification (I-IV), (Only if Clavien–Dindo classification is not available: anastomotic leakage (yes/no), Reoperation (yes/no), Any surgical Complication (yes/no), Any medical complication (yes/no));
- Operation time in minutes;
- Length of hospital stay in days;
- Resection status (R0, R1, R2, Rx);
- Number of harvested lymph nodes;
- Number of positive lymph nodes;
- Lymph node ratio (positive/total retrieved);
- Date of first flatus after intervention.

2.15. Data Synthesis

A random effects model with the restricted maximum likelihood estimator will be used in all meta-analyses [23]. In meta-analyses with at least five studies, we will use the Hartung–Knapp method which is not recommended for fewer studies [24]. We will present the main results in forest plots and Summary of Findings Tables according to the GRADE Tool. We will calculate 3- and 5-year probabilities as well as hazard ratios for time-to-event outcomes, risk ratios for binary outcomes, and mean differences for continuous outcomes. In the case of different assessment tools or scales being used for an outcome, we will calculate the standardized mean difference.

We will evaluate statistical heterogeneity using a Chi-squared test and the I-squared statistic (heterogeneity: 0–40% = small, 30–60% = moderate, 50–90% = substantial, >75% = considerable). Heterogeneity will be further investigated in subgroup analyses (see below). Publication bias will be assessed using funnel plots. A test for funnel plot asymmetry will be conducted in meta-analyses with at least 10 studies [25]. In addition, we will perform a sensitivity analysis using the fixed effect model for all outcomes.

Subgroup and sensitivity analyses: With respect to the primary outcome 5-year overall survival we will conduct subgroup analyses, stratified for the study-level covariates type of resection (right hemicolectomy vs. extended right hemicolectomy), as well as for different characteristics of the single studies and co-/interventions (e.g., laparoscopic vs. robotic; hand-assisted vs. fully laparoscopic; fully minimal-invasive vs. converted resections; converted vs. fully open resections; post-operative-enhanced recovery pathway yes/no). Other subgroup analyses will be defined based on exploratory analyses of the available data. For all outcomes, we will perform sensitivity analyses by excluding studies with high risk of bias based on the risk of bias assigned to studies as described above. All statistical analyses with be conducted using R, Version R-4.3.2 (R Core Team, Vienna, Austria) [26]. The incorporation of the risk of bias assessment into the analysis will be conducted via sensitivity analysis based on the risk of bias judgements of specific outcomes.

2.16. Reporting and Amendments

This IPD will be reported according to the Cochrane PRISMA-IPD checklist. In case of amendments to this protocol, all adjustments and their rationale will be updated in the PROSPERO registration and reported in the final publication.

3. Discussion

The role of surgery as the primary therapeutic intervention for colon cancer is pivotal. Right-sided compared to left-sided colon cancer is associated with lower survival rates [27]; however, recent meta-analyses have shown the potential of minimally invasive techniques in these patients [11,12]. Locally advanced stage III cancer (UICC III) could not be analyzed separately, in spite of being of particular interest, as this subgroup still suffers from less favorable outcomes [17]. This protocol outlined here delineates a structured approach to conducting a systematic review and individual patient data (IPD) meta-analysis to scrutinize and compare the oncological outcomes of minimally invasive and open surgery approaches specifically in patients with UICC stage III right-sided colon cancer, as this subset is associated with a less favorable prognosis compared to left-sided colon cancers. The technique of using individual patient data is deemed particularly valuable when the results of published studies fall short of enabling a comprehensive analysis [19]. This applies to this topic, as studies on patients with both UICC stage III disease and right-sided colon cancer are still lacking and there is insufficient outcome data reported for this particular subgroup in studies with broader cohorts. Instead, both aspects are usually analyzed separately. These circumstances make a conventional summary endpoint meta-analysis impossible. Thus, to answer this critical question, an IPD is necessary. This technique yields several additional advantages including the ability to explore heterogeneity, incorporate patient-level covariates while minimizing bias [19,28–30].

Limitations

As the research team is expecting to obtain too little data from RTC data alone for this specific subgroup of patients, the scope of our search was opened to quasi-randomized controlled clinical trials (CCTs). Depending on the quality of CCTs found to be eligible this might be the biggest limitation to the reliability of the results of this meta-analysis based on an increased selection bias. However, the research team aims to prevent an underpowered analysis and moreover will take account of this limitation by using sensitivity and subgroup analyses accordingly.

In this IPD, we can only investigate a selection of defined parameters that influence the outcome after colon cancer surgery. However, there might be several more patient factors and co-interventions that are beyond the scope of this review. Examples are the use of adjuvant chemotherapy, as well as surgical standards and perioperative care that differ between countries and might have changed over time since the publication of the original research. This specifically applies to fast-track recovery programs, that were

introduced in many hospitals within the last two decades with potential influence on oncological outcome.

The review team has decided that robotic surgery and single- and multi-port laparoscopic surgery, as well as hand-assisted and laparoscopic-assisted surgery will be included in the minimally invasive surgery group for this analysis. However, the comparability of these procedures is still under debate and further research is needed to eventually clarify whether it is appropriate to combine these procedures in one intervention group.

Like all IPDs, there is a certain risk that the review group will not be able to obtain enough individual patient data for an appropriate analysis. In this case the lack of data and reasons for it will be reported.

Author Contributions: F.H., C.R., S.S. and J.R. planned the protocol design. J.R. wrote the protocol, except for the data synthesis section which was revised by S.H. and G.S. All authors contributed to the protocol. The information sources and search strategy sections were written by M.G. and F.H.; S.B., S.S. and C.R. made subsequent comments and contributions to protocol drafts. S.L. contributed to the study selection process. G.S. contributed specific expertise regarding systematic reviews and IPD-methodology and data handling. F.H. is the guarantor of this review. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data from this study will be available from the corresponding author on reasonable request.

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Conflicts of Interest: All authors declare no financial conflict of interest. The team of researchers (explicitly the certified colorectal surgeons S.B., C.R., and F.H.) is practicing and teaching the minimally invasive technique as a standard for oncological right hemicolectomy in their institutions. This clear preference might represent a conflict of interest in favor of this MIC-approach regarding oncological right hemicolectomy.

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