Guideline Protocol

EAES Rapid Guideline: Complete Mesocolic Excision for Right-Sided Colon Cancer

with participation of SAGES and ESCP

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Conflict of interest statement

The authors declare no direct or indirect conflicts of interest. SAA has participated as panel member in a EAES/SAGES guideline on the management of diverticular disease.

INTRODUCTION

Background

Complete mesocolic excision (CME) is a surgical technique for the resection of right-sided colon cancer. It involves resection of the primary tumour combined with the excision of an intact mesocolon, exposure of the superior mesenteric vein (SMV) and central vascular ligation (CVL) [1. Tejedor P, Francis N, Jayne D, Hohenberger W, Khan J; on behalf the CME Project Working Group. Consensus statements on complete mesocolic excision for right-sided colon cancer-technical steps and training implications. Surg Endosc. 2022;36(8):5595-5601. doi:10.1007/s00464-021-08395-0], which has been postulated to achieve better oncological clearance, improved disease-free survival rates, and reduced local recurrence rates compared to standard right colectomy [Wang C, Gao Z, Shen Z, et al. Five-Year Prognosis of Complete Mesocolic Excision in Patients with Colon Cancer: A Prospective, Nonrandomized, Double-Blind Controlled Trial. J Am Coll Surg. 2022;235(4):666-676. doi:10.1097/XCS.0000000000000282; Kong JC, Prabhakaran S, Choy KT, Larach JT, Heriot A, Warrier SK. Oncological reasons for performing a complete mesocolic excision: a systematic review and meta-analysis. ANZ J Surg. 2021;91(1-2):124-131. doi:10.1111/ans.16518].

CME offers potential benefits in terms of accurate staging and improved pathological study, leading to a more accurate assessment of lymph node involvement, tumor margins, and other histopathological factors that guide the selection of appropriate adjuvant therapies, facilitating personalised treatment plans. However, there has been some controversy regarding the appropriateness of routine implementation of CME. The technique requires a high level of surgical expertise and meticulous attention to the anatomical details. The extensive dissection involved may increase the complexity and duration of the procedure, potentially leading to longer operating times and increased surgical risks [3. Kong JC, Prabhakaran S, Choy KT, Larach JT, Heriot A, Warrier SK. Oncological reasons for performing a complete mesocolic excision: a systematic review and meta-analysis. ANZ J Surg. 2021;91(1-2):124-131. doi:10.1111/ans.16518].

The adoption of CME as a standard technique requires surgeons to undergo specialised training and gain proficiency in the procedure. However, the learning curve associated with CME is steep, and not all surgeons may have access to appropriate training opportunities or mentorship. As a result, there can be variations in the implementation of CME across different surgical centers, potentially impacting the consistency and quality of surgical outcomes. Moreover, while there is broad agreement on the general principles of CME, there is still some debate regarding the specific technical aspects of the procedure [1]. Varying opinions and preferences among surgeons can lead to differences in practice, making it challenging to establish a standardised approach to CME.

The radical nature of this procedure can also lead to a higher likelihood of postoperative complications, such as anastomotic leaks or wound infections [3]. Critics of CME raise concerns about the potential increase in surgical morbidity, such as postoperative complications, longer operative times, and increased blood loss [1]. Additionally, the impact of CME on functional outcomes, such as bowel function, quality of life, and long-term complications, remains an area of ongoing research and debate.

Objectives

In this guideline, our aim is to provide evidence-based recommendations on CME for the management of right-sided colon cancer. By providing healthcare professionals with the necessary knowledge, we aim to improve patient care and surgical decision-making in the management of right-sided colon cancer.

Through a balanced understanding of the advantages and disadvantages of CME, surgeons can make informed decisions tailored to individual patient needs, ultimately optimising perioperative and long-term treatment results, including quality of life.

METHODS

Guideline Development Process

The guideline proposal was registered on the International Guidelines Library [International Guidelines Library. Available in: https://guidelines.ebmportal.com/eaes-rapid-guideline-complete-mesocolic-excision-right-sided-colon-cancer. Accessed 3 October 2023]. This protocol adheres to the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) [Guyatt GH, Oxman AD, Schunemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. J Clin Epidemiol. 2011;644:380–82.], Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) [Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA; PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;350:g7647. doi: 10.1136/bmj.g7647. Erratum in: BMJ. 2016 Jul 21;354:i4086. PMID: 25555855.], and AGREE-S (Appraisal of Guidelines for Research and Evaluation II) [Logullo P, Florez ID, Antoniou GA, Markar S, López-Cano M, Silecchia G, Tsokani S, Mavridis D, Brouwers M, Antoniou SA; GAP Consortium. AGREE-S: AGREE II extension for surgical interventions - United European Gastroenterology and European Association for Endoscopic Surgery methodological guide. United European Gastroenterol J. 2022 May;10(4):425-434. doi: 10.1002/ueg2.12231. Epub 2022 May 4. PMID: 35506366; PMCID: PMC9103371.] standards.

EAES members will have the opportunity to provide their input on the content through social media and the email newsletter. Comments received will be considered and incorporated into the protocol through amendments.

Funding

The guideline is supported and financially sponsored by EAES. The funding entity will not exert any influence on the development of the guideline.

Steering Group

The steering group will consist of a certified master guideline developer and chair and a colorectal surgeon, both without financial nor indirect conflicts of interest.

Guideline methodologist

The methodological aspect of this guideline will be overseen by a certified master guideline developer and chair (International Guideline Development Credentialing & Certification Program - INGUIDE certificate number: 2022-L3-V1-00014) who has extensive experience in evidence synthesis and has actively contributed to the development of over 15 clinical practice guidelines. In addition, 2 trainee methodologists who are completing INGUIDE certification will be assisting in the process.

Guideline panel and external advisors

The panel for this guideline will consist of 7 surgeons, 2 oncologists, one pathologist, and one patient representative. Contributions of panel members and external advisors will be recognised through authorship in the journal publication of the guideline report.

Guideline questions

The guideline will address the following healthcare question:

Should CME be preferred over standard right hemicolectomy for right-sided colon cancer?

Subgroup analyses will aim to address cancers of the cecum, the ascending colon, and the hepatic flexure.

Outcome Selection and Determination of Utility Values

The steering group will draft a list of potential outcomes. To identify outcomes of interest and establish minimal important differences, panel members will independently assess the importance of each outcome using the GRADE scale.[20] They will also have the opportunity to propose additional outcomes considered significant or critical. The steering group will calculate the median score for each outcome to identify important (score 4-6) and critical (score 7-9) items for inclusion. If substantial variation is obtained among panel evaluations of outcomes, a synchronous meeting will be held online to resolve conflicts and reach consensus.

The steering group will ask panel members to provide their judgements on the utility of each outcome, with 0 the worst possible health state/death, and 10 the best possible health state.

We will present questions such as “What do you consider is the utility value of major postoperative complications (Clavien-Dindo ≥3b; eg reoperation, abdominal abscess requiring drainage)? Utility represents the strength for an individual's preference for a given outcome. Zero reflects states of health equivalent to death/worst imaginable health, and 10 reflecting perfect health/best imaginable health.” We will select the median utility value for each outcome unless there is significant variation in responses, in which case a synchronous, online meeting will be hosted by the master guideline developer to achieve consensus among panel members.

Utility values will be conversed to coefficients according to the equation Coefficient = Absolute Risk Difference * (1 - Utility). We will compare these values with research-informed anchors indicating trivial-to-small effect threshold (0.0135), small-to-moderate effect threshold (0.0321), and moderate-to-large effect threshold (0.0625). We will also aggregate these values (positive and negative). The judgements on the effect sizes of each outcome and the aggregate value will inform discussions on the evidence-to-decision framework and the net benefit or harm/burden [Wiercioch W. Defining decision thresholds for judgments on health benefits and harms using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Evidence to Decision (EtD) frameworks: a randomised methodological study (GRADE-THRESHOLD). Presented at the GIN 2023 Conference, Glasgow, 19-22 September 2023]. The outcomes will be considered within a fully contextualized evidence-to-decision process.

Literature Search

The guideline methodologist and the trainee methodologists have developed a comprehensive literature search strategy to identify relevant studies and evidence (see Appendix). An experienced systematic reviewer will oversee the search process, data extraction and risk of bias assessment, that will be conducted by 2 surgeons or surgeons-in-training with experience in conducting systematic reviews. We have performed a scoping search to evaluate the availability of randomized trials and observational studies that address our question framework. Our search will focus on original articles published in English from 2008 onwards, since the CME technique was first described by Hohenberger and colleagues in that year [Hohenberger W, Weber K, Matzel K, Papadopoulos T, Merkel S. Standardized surgery for colonic cancer: complete mesocolic excision and central ligation--technical notes and outcome. Colorectal Dis. 2009;11(4):354-365. doi:10.1111/j.1463-1318.2008.01735.x]. Two systematic reviewers will independently screen the records in a blinded manner using the Rayyan platform [Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev. 2016 Dec 5;5(1):210. doi: 10.1186/s13643-016-0384-4. PMID:27919275; PMCID: PMC5139140]. Any potential conflicts will be resolved through discussion after revealing the screening results, and if any disagreements persist, the systematic review coordinator will take the final decision. The same reviewers, in collaboration with the systematic review coordinator, will conduct a full-text screening of selected articles. They will extract relevant data from selected studies that meet the inclusion criteria related to study characteristics, patient populations, and outcome data in a duplicated manner, with any discrepancies being resolved by the systematic review coordinator. We will organize the extracted data in a standardized format for further analysis. We will assess the risk of bias in randomized trials using RoB 2.0, and in comparative cohort studies using ROBINS-I [Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng HY, Corbett MS, Eldridge SM, Emberson JR, Hernán MA, Hopewell S, Hróbjartsson A, Junqueira DR, Jüni P, Kirkham JJ, Lasserson T, Li T, McAleenan A, Reeves BC, Shepperd S, Shrier I, Stewart LA, Tilling K, White IR, Whiting PF, Higgins JPT. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019 Aug 28;366:l4898. doi: 10.1136/bmj.l4898. PMID: 31462531; Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I, Carpenter JR, Chan AW, Churchill R, Deeks JJ, Hróbjartsson A, Kirkham J, Jüni P, Loke YK, Pigott TD, Ramsay CR, Regidor D, Rothstein HR, Sandhu L, Santaguida PL, Schünemann HJ, Shea B, Shrier I, Tugwell P, Turner L, Valentine JC, Waddington H, Waters E, Wells GA, Whiting PF, Higgins JP. ROBINS-I: a tool for assessing risk of bias in nonrandomised studies of interventions. BMJ. 2016 Oct 12;355:i4919. doi: 10.1136/bmj.i4919. PMID: 27733354; PMCID: PMC5062054.]. We will perform the risk of bias assessment for each outcome or group of outcomes with similar follow-up features (such as timing and assessment methods). We will provide detailed judgments on the risk of bias, and we will use the Robvis tool to summarise these judgments.

Inclusion criteria

We will include studies comparing laparoscopic or robotic right hemicolectomy with complete mesocolic excision versus standard right hemicolectomy (as this is defined by study authors) for cancer of the cecum, ascending colon, or right hepatic flexure in adult patients.

Methodology for Evidence Synthesis

In a scoping search, we identified a small number of randomized clinical trials (RCTs) and matched cohort studies. Evidence from published randomized trials is not expected to provide sufficient certainty of

evidence (primarily due to small information size and few events). We will, therefore, search for both randomized and observational studies (OS). We will consider matched observational data only, to mitigate the risk of confounding bias. We will perform risk of bias assessments and consider a priori the following potential confounders as determinants of acceptable risk of bias (ROBINS I, confounding bias domain): American Society of Anesthesiologists score, body mass index, tumor location (cecum/ascending colon/hepatic flexure), tumor size. We will perform separate analyses of randomized and cohort studies. We will consider a joint analysis of randomized and observational studies as per INGUIDE principles (naive approach). A naive pooling method is identical to the conventional random-effects model since all studies are combined directly, regardless of their design. Finally, we will use the crossnma package, which can be used to combine RCTs with OS in network meta-analysis, with aggregate or individual patient data or a mixture of both. This method is straightly extended to meta-analysis [Tasnim Hamza, Guido Schwarzer and Georgia Salanti (2022). crossnma: Cross-Design and Cross-Format Synthesis using Network Meta-Analysis and Network Meta-Regression. R package version 1.0.1. https://github.com/htx-r/crossnma].

In the presence of substantial statistical or conceptual heterogeneity, we will use a random effects meta-analysis to quantitatively synthesize evidence [Borenstein, M., Hedges, L.V., Higgins, J.P. and Rothstein, H.R. (2010), A basic introduction to fixed-effect and random-effects models for meta-analysis. Res. Synth. Method, 1: 97-111. https://doi.org/10.1002/jrsm.12; Nikolakopoulou A, Mavridis D, Salanti G. How to interpret meta-analysis models: fixed effect and random effects meta-analyses. Evid Based Ment Health. 2014 May;17(2):64. doi: 10.1136/eb-2014-101794. PMID: 24778439]. For continuous outcomes, we will extract, if available, the sample size, mean outcome value, and corresponding standard deviation (SD) for each group or we will estimate them from any available hypothesis testing statistic (test, p-value, or confidence interval) if possible. We will estimate the mean difference (MD) or standardized mean difference (SMD) for each outcome if studies have used different scales to measure the same outcome.

For time-to-event data, we will extract hazard ratio estimates using statistics estimated from a long-rank analysis and/or use the reported p-value or confidence interval to calculate the estimated standard error, if the summary statistics for each study are not provided (hazard ratio (HR) and variance). Then, we will estimate the pooled logarithm HR along with its corresponding 95% confidence interval. As part of a sensitivity analysis, we will combine studies that provide HRs with others that provide RRs (or the number of events and sample size in each group), if they coexist. Also, we plan to calculate the absolute effects for time to event data for the GRADE Summary-of-Findings (SoF), according to the methods specified by Skoetz et al [Skoetz N, Goldkuhle M, van Dalen EC, Akl EA, Trivella M, Mustafa RA, Nowak A, Dahm P, Schünemann H, Bender R; GRADE Working Group. GRADE guidelines 27: how to calculate absolute effects for time-to-event outcomes in summary of findings tables and Evidence Profiles. J Clin Epidemiol. 2020 Feb;118:124-131. doi: 10.1016/j.jclinepi.2019.10.015. Epub 2019 Nov 9. PMID: 31711910.].

We will utilize the Restricted Maximum Likelihood (REML) estimator to determine the between-study variance [Veroniki AA, Jackson D, Viechtbauer W, Bender R, Bowden J, Knapp G, Kuss O, Higgins JP, Langan D, Salanti G. Methods to estimate the between-study variance and its uncertainty in meta-analysis. Res Synth Methods. 2016 Mar;7(1):55-79. doi: 10.1002/jrsm.1164. Epub 2015 Sep 2. PMID: 26332144; PMCID: PMC4950030]. Heterogeneity will be explored using the I2 statistic, which describes the percentage of variability in effect estimates attributed to heterogeneity rather than sampling error. Additionally, we will compute the Q-statistic and 95% predictive intervals to explore heterogeneity and determine the plausible range of effect size values for future trials [Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. BMJ. 2011 Feb 10;342:d549. doi: 10.1136/bmj.d549. PMID: 21310794]. We will assess small study effects either visually through funnel plot symmetry or

statistically using Egger's test. It has been suggested that a minimum of ten studies is necessary for Egger's test [Egger M, Smith G D, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test BMJ 1997; 315 :629 doi:10.1136/bmj.315.7109.629]. As a sensitivity analysis, we will apply the fixed effect model for each analysis where we have applied the random effects model.

We will conduct meta-analyses of proportions to calculate the baseline risk for each outcome, for the purposes of estimating absolute effect differences. We will use the R statistical package version 4.3.1, utilizing the meta and metafor packages [Balduzzi S, Rücker G, Schwarzer G (2019). "How to perform a meta-analysis with R: a practical tutorial." Evidence-Based Mental Health, 153–160. DOI: 10.1136/ebmental-2019-300117].

GRADE Summary of Findings

We will assess the certainty of the evidence from the meta-analysis using the GRADE approach [Guyatt G, Agoritsas T, Lytvyn L, Siemieniuk R, Vandvik P: BMJ Rapid Recommendations: A Possible Revolution in Clinical Practice Guidelines. Can J Gen Intern Med 2019;14(1):6-12]. This approach considers five domains of certainty: risk of bias, imprecision, indirectness, publication bias, and magnitude of effect. The methodologist will assess the certainty of the evidence for each domain and assign a rating of high, moderate, low, or very low. The results of the meta-analysis will be presented in a clear and transparent way using MAGICapp [MAGICapp. Available in: https://app.magicapp.org/#/guidelines. Accessed July 17th, 2023.].

Evidence to decision framework

The panel will receive GRADE evidence summaries and supporting material at least two weeks before the consensus meeting. The meeting will be held in person and will include a detailed presentation of the guideline development methodology. The panel will discuss the evidence summaries and the evidence-to-decision framework, and they will address any concerns or disagreements [Schünemann HJ, Al-Ansary LA, Forland F, Kersten S, Komulainen J, Kopp IB, Macbeth F, Phillips SM, Robbins C, van der Wees P, Qaseem A; Board of Trustees of the Guidelines International Network. Guidelines International Network: Principles for Disclosure of Interests and Management of Conflicts in Guidelines. Ann Intern Med. 2015 Oct 6;163(7):548-53. doi: 10.7326/M14-1885. PMID: 26436619.].

We will develop an evidence-to-decision frameworkto support the recommendation . The framework will consider the following factors [Alonso-Coello P, Schünemann HJ, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, Treweek S, Mustafa RA, Rada G, Rosenbaum S, Morelli A, Guyatt GH, Oxman AD; GRADE Working Group. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction. BMJ. 2016 Jun 28;353:i2016. doi: 10.1136/bmj.i2016. PMID: 27353417.]:

- Benefits and harms of the intervention and their balance (informed by utility-adjusted coefficients)
- Certainty of the evidence
- Values and preferences of patients and healthcare providers
- Resources required
- Acceptability of the intervention
- Feasibility of implementing the intervention
- Equity

Based on the evidence-to-decision framework, the panel will draft recommendation(s) in line with the GRADE methodology. External advisors will participate in the discussions, but they will not be involved in making judgments about the evidence-to-decision domains.

After the in-person meeting, panel members will vote on the direction and strength of the recommendation(s). They will also be able to suggest modifications to the formulation of the recommendations, as long as they agree with the GRADE methodology [Hultcrantz M, Rind D, Akl EA, Treweek S, Mustafa RA, Iorio A, Alper BS, Meerpohl JJ, Murad MH, Ansari MT, Katikireddi SV, Östlund P, Tranæus S, Christensen R, Gartlehner G, Brozek J, Izcovich A, Schünemann H, Guyatt G. The GRADE Working Group clarifies the construct of certainty of evidence. J Clin Epidemiol. 2017 Jul;87:4-13. doi: 10.1016/j.jclinepi.2017.05.006. Epub 2017 May 18. PMID: 28529184; PMCID: PMC6542664]. Consensus will be defined as agreement above 80% among panel members. In case of lack of consensus, this will be stated in the guideline report.

Target users

The guideline is aimed at surgeons, oncologists, primary healthcare physicians, policymakers, and patients. A patient-friendly version of the guideline will be developed.

Publication and dissemination strategy

The guideline will be published in the journal Surgical Endoscopy and Other Interventional Techniques, which is the official journal of the European Association for Endoscopic Surgery (EAES). The guideline will also be distributed through social media, letters to the editor, scientific meetings, and other channels.

Feedback

The steering group will consider feedback on the guideline report from a variety of sources, including social media, letters to the editor, and other feedback mechanisms. This will be considered in future updates to the guideline.

Monitoring, update, and future steps

The use of the guideline will be reviewed by EAES members two years post-publication via an online survey. Updates to the guideline will be made under the guidance of the steering committee, based on the availability of new literature on the topic.

Implications for practice and research

The goal of this guideline is to provide up-to-date recommendations on the application of the CME principles for right-sided colon cancer resections. These guidelines are intended to assist patients, surgeons, and other healthcare professionals in making decisions and informing policy-making. The systematic review, meta-analysis and the evidence-to-decision framework are also expected to identify areas where research is needed and fill evidence gaps.

Strengths and limitations

This guideline follows a transparent and reproducible process for the systematic assessment of evidence, based on the GRADE methodology. It considers patient values and preferences in the development of

recommendations, while involving a multidisciplinary expert panel. This leads to well-informed and balanced recommendations.

However, the guideline may have some limitations. The interpretation of available evidence can be subjective and open to varying perspectives. The combination of various study designs and outcomes can introduce heterogeneity, making it challenging to draw definitive conclusions. Additionally, the guideline may not always fully consider individual patient characteristics or unique clinical scenarios. Despite the systematic approach, some clinical questions may still need to be answered or fully addressed.

The rapid review process has also been documented to have some limitations. These include inconsistency in research techniques and reporting, as well as variation in the definitions of rapid reviews. However, there is also evidence to suggest that rapid reviews can produce conclusions similarto those of systematic reviews. They also offer other benefits, such as faster research time, more efficient use of resources, and an overview of evidence on a particular topic. Consequently, rapid reviews are seen to play an important role in the production of policy guidelines and the support of decision-making.

Research ethics

All members of the guideline development group will disclose any direct (financial) or indirect (intellectual) conflicts of interest. We will manage conflicts according to the principles of the Guidelines International Network (GIN). Members with relevant direct or indirect conflicts will participate as external advisors, and they will not be involved in discussions about the direction or strength of the recommendations, the voting procedure, or the Delphi process to consolidate the recommendations.

CONCLUSION

This guideline aims to provide trustworthy, evidence-informed recommendations on the use of CME in the resection of right-sided colon cancer, to help healthcare professionals and other stakeholders in making the best decisions for their patients.

APPENDIX

Search syntax

(cme[ti] OR (complete mesocolic excision[ti]) OR D3[ti]) AND (right[ti] OR right-sided[ti] OR cecal[ti] OR caecal[ti] OR cecum[ti] OR caecum[ti] OR ascending[ti] OR (hepatic flexure[ti]))