GUIDELINE PROTOCOL

EAES Multidisciplinary Rapid Guideline: Systematic review, meta-analysis, GRADE assessment and evidence-informed recommendations on the surgical management of paraesophageal hernias

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Conflicts of interest

The authors declare no direct (financial) conflicts of interest. Stavros A. Antoniou and Sheraz Markar have published evidence syntheses on the topic of this rapid guideline.

Funding

This project is funded by the *European Association for Endoscopic Surgery and Other Interventional Techniques* (EAES).

INTRODUCTION

Background

Paraesophageal hernia is a condition presenting with fairly high prevalence, especially in advanced age. It may be asymptomatic, or present with a wide range of signs and symptoms, such as heartburn, dyspnea, anemia, and pain. The heterogeneous features of paraesophageal hernias suggest that its management should be tailored. There is a number of debated management options, that refer to surgical intervention or 'wait and watch' strategy, the use of mesh for augmentation of the hiatus, and the management of the stomach following hernia reduction.

There are no recent guidelines on the management of paraesophageal hernias, and previous recommendations may not be pertinent in the light of new evidence *[1]*. A survey of *European Association for Endoscopic Surgery* members indicated that this topic is prioritized by a substantial proportion of European surgeons *[2]*.

Objectives

The aim of this rapid guideline is to support healthcare professionals (surgeons, gastroenterologists, primary care physicians) and patients in navigating clinical decision making around the management of paraesophageal hernias, with the objective to improve perioperative and long-term outcomes, including the quality of life.

METHODS

This protocol follows applicable AGREE-S and PRISMA-P reporting standards *[3,4]*. EAES members will be invited to comment on the content through social media and email newsletter, and constructive comments will be addressed through amendment of this protocol.

Funding

The guideline is sponsored and funded by EAES. The funding body will have no influence on the development of the guideline.

Steering Group

The steering group consists of a surgeon with expertise in upper gastrointestinal surgery and a general surgeon and certified guideline methodologist, chair of the EAES Guidelines Subcommittee.

Guideline methodologist

A certified guideline methodologist (INGUIDE certificate number 2021-L2-V1-00001) who has participated in the development of more than 15 clinical practice guidelines and with vast experience in evidence synthesis will lead this work from the methodological aspect.

Guideline panel and external advisors

We will include 5 surgeons, one gastroenterologist and one patient representative as panel members. At least half of the panel members will have been certified by an official certification body (INGUIDE certification program). We will recruit 3 opinion leaders as external advisors, in line with Guidelines International Network standards *[5]*. Panel members' and external advisors' contributions will be acknowledged through authorship in the journal publication of the guideline report.

Guideline questions

The guideline will address three healthcare questions:

1. Should asymptomatic/minimally symptomatic paraesophageal hernias be managed conservatively or with surgery?
2. Should a mesh versus sutures only be used for closure of the hiatus in paraesophageal hernia repair?
3. Should a gastropexy versus a Nissen or Toupét operation be performed in paraesophageal hernia repair?

Selecting outcomes of interest and setting minimal important differences

The steering group will make a list of candidate outcomes. Panel members and external advisors will vote on the importance of the outcomes using the GRADE scale *[6]*, and propose additional important or critical outcomes. The median score for each outcome will be calculated, and important (score 4-6) and critical (score 7-9) items will be selected. In case there is wide variation in panel members' and external advisors' judgements (i.e., insufficient importance and critical importance for a given outcome), they will have an online meeting steered by the methodologist to discuss their judgements and arrive at consensus. We will make every effort to prioritize patient-important outcomes and limit the number of outcomes, as per Cochrane guidance *[7]*.

Furthermore, panel members and external advisors will be asked to set minimal important differences per outcome, following a fully contextualized approach *[8]* (e.g., "If 'major complications' was the only outcome of interest, which difference between conservative and surgical management would be clinically important"), with multiple choice responses (e.g., 5 out of 1000; 10 out of 1000, etc.), and the option to provide a different response. We will select the median minimal important difference for each outcome, unless there is substantial variation in responses, in which case panel members will convene online to reach consensus under the guidance of the methodologist.

Systematic review

The guideline methodologist has developed separate search strategies for each question framework (**Appendix 1**) after a scoping search of PubMed to assess the availability of randomized trials or observational studies on each clinical question. We will search PubMed for original articles addressing the question frameworks, published from 1990 onwards in the English language. Two systematic reviewers will screen the records in a blinded manner using the platform *Rayyan [9]*. Conflicts will be resolved by discussion after unblinding, and the methodologist will adjudicate remaining disagreements. The same reviewers in collaboration with the methodologist will select articles based on full text screening. They will extract study and patient population characteristics, and outcome data in duplicate; the first author will resolve disagreements. We will assess risk of bias in randomized trials using RoB 2.0, and in observational studies using ROBINS-I, per outcome or per group of outcomes, if these share similar follow-up features (e.g., timing and method of assessment) *[10,11]*. We will provide detailed risk of bias judgements and we will summarize these using the *robvis* tool *[12]*.

Evidence synthesis methodology

Statisticians, members of the EAES Guidelines Subcommittee, with expertise in advanced evidence synthesis and guideline development will perform statistical analyses independently. We will perform meta-analysis of randomized trials and/or observational studies. In our experience, the certainty of the evidence from randomized trials in the field of surgery is almost invariably moderate or lower. Similarly, the certainty of the evidence from observational studies is below moderate (i.e., low or very low). We will therefore use observational evidence when less than 3 trials provide evidence on an outcome, in line with the complementary GRADE approach *[13]*. If the direction of the effect per outcome is similar between randomized and observational studies, we may consider the summary effect estimate of randomized and observational studies with separate analyses of randomized and observational studies.

In the absence of heterogeneity between randomized and observational evidence, we will consider the overall effect estimates.

We will conduct a random effect meta-analysis *[14,15]* to synthesize quantitatively the evidence for the three aforementioned research questions since we expect much variation in the PICO criteria across trials. For the binary outcomes, we will extract the number of events and the sample size of each group, and we will estimate for each outcome the odds ratio (OR) along with the corresponding 95% confidence interval (CI). A continuity correction will be applied to the studies with zero-cell counts. For the continuous outcomes, we will extract the sample size, and the mean effect with the corresponding standard deviation (SD) for each group, if it is available. We will estimate for each outcome the mean difference (MD) or the standardized mean difference (SMD) if different scales were used to measure the same outcome among studies. We will use the Restricted Maximum Likelihood (REML) *[16]* estimator for the between study-variance (heterogeneity). We will explore heterogeneity via the I^2 statistic that describes the percentage of the variability of effect estimates, that is due to heterogeneity rather than sampling error. We will further explore heterogeneity by computing the Q-statistic and the 95% predictive intervals *[17]* that show the plausible range of effect size values for a future trial. We also plan to check for small study effects, either visually by inspecting the symmetry of the funnel plot, or statistically by applying Egger's test. It has been suggested that at least ten studies are needed for the Eggers' test *[18]*. The fixed effect (also known as common effect) model will be applied for all analyses as a sensitivity analysis. In the case that we will have both Observational Studies (OS) and Randomized Clinical Trials (RCTs) for an outcome, we will meta-analyze the two types of studies separately and if the results are in agreement, we will perform also a meta-analysis with both types of studies. Additionally, we will run proportion meta-analyses to calculate the baseline risk of each outcome. Analyses will be performed in R statistical package version 4.0.3 using the meta, metafor packages *[19]*.

Evidence appraisal

Results of evidence syntheses will be summarized in evidence tables on MAGICapp *[20]*. The certainty of the evidence will be assessed by the methodologist on the domains of risk of bias, imprecision, indirectness, publication bias and magnitude of effect. Judgements on risk of bias will be considered in the context or relevant GRADE guidance *[21]*. Judgements on imprecision will be informed by the summary of decision thresholds set by the panel members and external advisors (see *Selecting outcomes of interest and setting minimal important differences*). We will explore for any sources of heterogeneity; if heterogeneity can be conceptually explained, we will not downgrade the certainty of evidence for this factor.

Evidence to decision framework

We will make the evidence summaries, along with supporting material (e.g., risk of bias assessment, primary studies) available to panel members and external advisors at least 2 weeks before the consensus meeting. This will take place in person, and it will involve detailed presentation of the guideline development methodology, addressing any concerns or disagreements by the panel and the external advisors regarding the evidence summaries, and the evidence to decision framework.

Separate evidence-to-decision frameworks will be developed for each clinical question. These will involve discussion on:

- benefits and harms
- certainty of the evidence
- values and preferences
- resources
- acceptability
- feasibility
- equity

Under consideration of the evidence-to-decision discussion and relevant judgements, the panel will draft recommendations in line with the GRADE methodology *[22]*. External advisors will participate in the discussions, but they will not be involved in the judgements on the evidence-to-decision domains *[5]*. In an online survey and Delphi process after the in-person meeting, panel members will vote on the direction and the strength of the recommendations, and will be able to suggest modifications to the formulation of the recommendations, which must agree with the GRADE methodology to be considered. Consensus will be defined as agreement above 80% among panel members.

Target users

The guideline is targeted at surgeons, gastroenterologists, primary healthcare physicians, policy makers, and patients. A patient version of the manuscript written in lay language will accompany the guideline report.

Publication and dissemination strategy

This guideline is funded and sponsored by EAES and will be submitted for publication in *Surgical Endoscopy and Other Interventional Techniques*, official journal of the Association.

Feedback

The steering group will take cognizance of constructive comments on the guideline report through social media, letters to the editor and other, and consider such feedback in future updates of the guideline.

Monitoring, update and future steps

The use of the guideline will be reviewed by EAES members at 2 years post publication via an online survey. Updates of the guideline will be under the guidance of the steering committee, based on availability of new literature on the topic.

DISCUSSION

Implications for practice and research

The aim of the guideline is to provide up to date recommendations using a rapid review research strategy on the management of paraesophageal hernia, to guide clinical practice and assist in patient care. Guidelines are expected to assist patients', surgeons' and other healthcare professionals' decision making and inform policy making. The systematic review and meta-analysis are also expected to offer insight into areas of development in research, identifying substantial evidence gaps or insufficiencies.

Strengths and limitations

There are documented limitations associated with the rapid review process, including lack of consistency across research techniques and reporting, as well as variation in the definitions associated with rapid reviews. There is also evidence to support rapid reviews as having similar conclusions to systematic reviews and other benefits such as accelerated time to conduct research, better use of resources and gaining an overview of evidence on a particular topic *[23-25]*. As such, the rapid review process is identified as having an important role in producing policy guidelines and supporting decision making.

Research ethics

All members of the guideline development group will declare any direct (financial) or indirect (intellectual) conflicts of interest. Conflicts will be managed according to Guidelines International Network principles; members with relevant direct or indirect conflicts will participate as external advisors, with no participation in the discussions about the direction and the strength of the recommendations, nor the voting procedure or the Delphi process to consolidate the recommendations. Both members of the steering group have published evidence syntheses on the topics to be discussed

in this guideline, which may be considered and indirect conflict. Their last evidence synthesis work was published more than 7 years ago *[26,27]*, and substantial new evidence has emerged since; therefore, we do not consider this to have an impact on the content of the guideline.

CONCLUSION

The rapid guideline will provide evidence-based recommendations on paraesophageal hernia management with a view to assist clinical decision making.

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APPENDIX

Search syntaxes

Question 1. Should asymptomatic or minimally symptomatic paraesophageal hernias be managed conservatively or with surgery?

(paraesophageal OR paraoesophageal OR para-esophageal OR para-oesophageal OR hiatal OR hiatus) AND hernia AND (surgery OR fundoplication OR gastropexy) AND ((watchful waiting) OR conservative OR non-operative)

Question 2. Should a mesh versus sutures only be used for closure of the hiatus in paraesophageal hernia repair?

((paraesophageal OR paraoesophageal OR para-esophageal OR para-oesophageal OR hiatal OR hiatus) AND hernia AND (mesh OR prosthetic OR reinforcement)) AND ((randomized controlled trial [pt]) OR

(controlled clinical trial [pt]) OR (randomized [tiab]) OR (placebo [tiab]) OR (drug therapy [sh]) OR (randomly [tiab]) OR (trial [tiab]) OR (groups [tiab]) NOT (animals [mh] NOT humans [mh]))

Question 3. Should a gastropexy versus a Nissen or Toupét operation be performed in paraesophageal hernia repair?

(paraesophageal OR paraoesophageal OR para-esophageal OR para-oesophageal OR hiatal OR hiatus) AND hernia AND ((Nissen OR Toupét OR Toupet OR 360 OR 270 OR total OR partial) AND fundoplication) AND (gastropexy OR Hill OR (anterior repair))