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Original Article

Anastomotic leak following oesophagectomy: research priorities from an international Delphi consensus study

Oesophago-Gastric Anastomosis Study Group on behalf of the West Midlands Research Collaborative*

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Abstract

Background: The Oesophago-Gastric Anastomosis Audit (OGAA) is an international collaborative group set up to study anastomotic leak outcomes after oesophagectomy for cancer. This Delphi study aimed to prioritize future research areas of unmet clinical need in RCTs to reduce anastomotic leaks.

Methods: A modified Delphi process was overseen by the OGAA committee, national leads, and engaged clinicians from high-income countries (HICs) and low/middle-income countries (LMICs). A three-stage iterative process was used to prioritize research topics, including a scoping systematic review (stage 1), and two rounds of anonymous electronic voting (stages 2 and 3) addressing research priority and ability to recruit. Stratified analyses were performed by country income.

Results: In stage 1, the steering committee proposed research topics across six domains: preoperative optimization, surgical oncology, technical approach, anastomotic technique, enhanced recovery and nutrition, and management of leaks. In stages 2 and stage 3, 192 and 171 respondents respectively participated in online voting. Prioritized research topics include prehabilitation, anastomotic technique, and timing of surgery after neoadjuvant chemo(radio)therapy. Stratified analyses by country income demonstrated no significant differences in research priorities between HICs and LMICs. However, for ability to recruit, there were significant differences between LMICs and HICs for themes related to the technical approach (minimally invasive, width of gastric tube, ischaemic preconditioning) and location of the anastomosis.

Conclusion: Several areas of research priority are consistent across LMICs and HICs, but discrepancies in ability to recruit by country income will inform future study design.

Introduction

Anastomotic leaks after oesophagectomy have a reported incidence ranging from 6 to 20 per cent[1–3] and are associated with major mortality rates of between 8 and 19 per cent[1–4]. Anastomotic leaks are associated with increased hospital costs, increased likelihood of anastomotic stricture[5], and reduced long-term survival[6–8]. The international Oesophagogastric Anastomosis Audit (OGAA)[9] identified variation in clinical practice and outcomes after oesophagectomy for cancer, highlighting the need to improve the current evidence base[10].

Currently, strategies for prevention and management of anastomotic leaks vary across centres internationally[11–14], owing to a lack of high-quality RCTs. RCTs have focused on anastomotic techniques[15,16], omentoplasty[17], extent of lymphadenectomy[18], and surgical approaches[19,20]. Even then, adoption of these techniques within clinical practice remains an ongoing debate because of lack of quality assurance systems[21,22]. Hence, streamlining research efforts to reduce anastomotic leaks will help improve the current evidence base.

Although research prioritization exercises exist within surgery[23], they are lacking in this area. A research prioritization exercise was therefore undertaken, using modified Delphi consensus methodology among international oesophageal surgeons, aiming to identifying optimal areas to target with future research in preventing and management of anastomotic leaks after oesophagectomy, and to determine the feasibility of recruiting patients into such studies.

Methods

The modified Delphi methodology has been described previously[23–25]. Starting from an initially broad range of ideas and themes, the process was planned to deliver consensus on the highest research priorities. A three-stage consensus process was designed for this priority-setting exercise, including two rounds of voting (*Fig. 1*).

Stage 1: evidence-base mapping

Evidence-base mapping was performed by two authors on the 20 September 2019 using PubMed, Embase and the Cochrane Library to identify relevant RCTs on interventions to reduce anastomotic leaks after oesophagectomy for cancer. The search terms used were ‘anastomotic leaks’ or ‘leaks’ and, ‘oesophagectomy’, or ‘oesophagogastrectomy’ and ‘randomised’, or ‘randomized, or ‘randomised controlled trials’ individually, or in combination. Inclusion criteria were: RCTs reporting risk factors for

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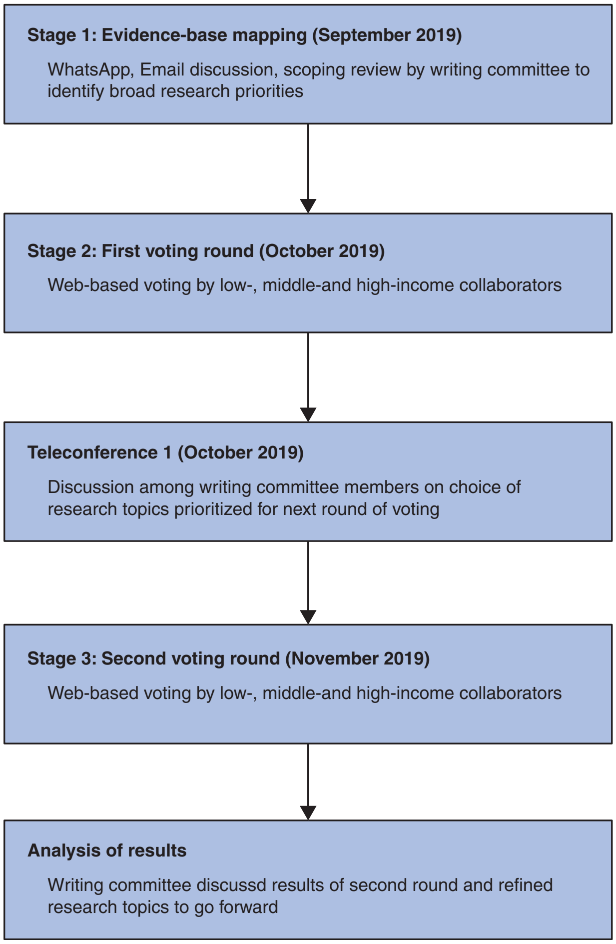

Fig. 1 Overview of Delphi process for prioritizing research for interventions to reduce anastomotic leaks after oesophagectomy

anastomotic leaks in human subjects undergoing oesophagectomy for cancer; systematic reviews and meta-analyses; and articles published in the English language. After excluding duplicates, two researchers independently reviewed the full texts of identified studies. Reference lists of all included studies were hand searched to identify other potentially relevant studies. Identified topics were then grouped into six broad research themes: preoperative optimization, surgical oncology, technical approach, anastomotic technique, enhanced recovery and nutrition, and management of leaks.

Stages 2 and 3: first and second voting round

A survey consisting of 27 questions was developed and distributed to surgeons from the OGAA collaborative and advertised through specialty organizations' social media accounts (such as Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland, European Society for Diseases of the Esophagus, and International Society for Diseases of the Esophagus). Specific criteria for participation included surgeons who perform resections either independently, supervised, or assisting (consultants and senior trainees).

Each question asked the respondent to rank each research question in terms of priority for future research into anastomotic leak prevention and management, and then for ability to recruit. For each research question, both priority and ability to recruit were scored using a Likert scale from 1 to 5 (1, low priority; 3, neutral; 5, high priority). A free-text comment box was also available at the end of each statement, and an additional section in round 1 of the Delphi questionnaire was included for participants to provide suggestions for further research. Two complete rounds were conducted for this Delphi study. Results from the first round were analysed, and any suggestions for future research expressed in the free-text section in round 1 were considered by the steering committee for inclusion in the second round (*Table S1*). Only complete questionnaires were used in the final analysis and duplicate responses from the same respondent were excluded. After the second round of voting, the priority of topics was quantified by the mean Likert score, with the top 10 topics classified as high priority.

Survey administration

The survey was administered online using the Research Electronic Data Capture (REDCap) system hosted by the Birmingham Surgical Trials Consortium at the University of Birmingham. Participation in the study was voluntary, with no financial or other remuneration offered. Two reminder e-mails were sent to participants at 2-week intervals after each round of voting. All results and feedback were anonymized, so no individual or institution could be identified.

Statistical analysis

Cronbach's α was chosen as the statistical test to evaluate consensus quantitatively among the international expert panel; a Cronbach's α value of at least 0.80 was representative of an acceptable measure of internal reliability[26–29]. Categorical variables were compared using the χ^2 test. Non-normally distributed data

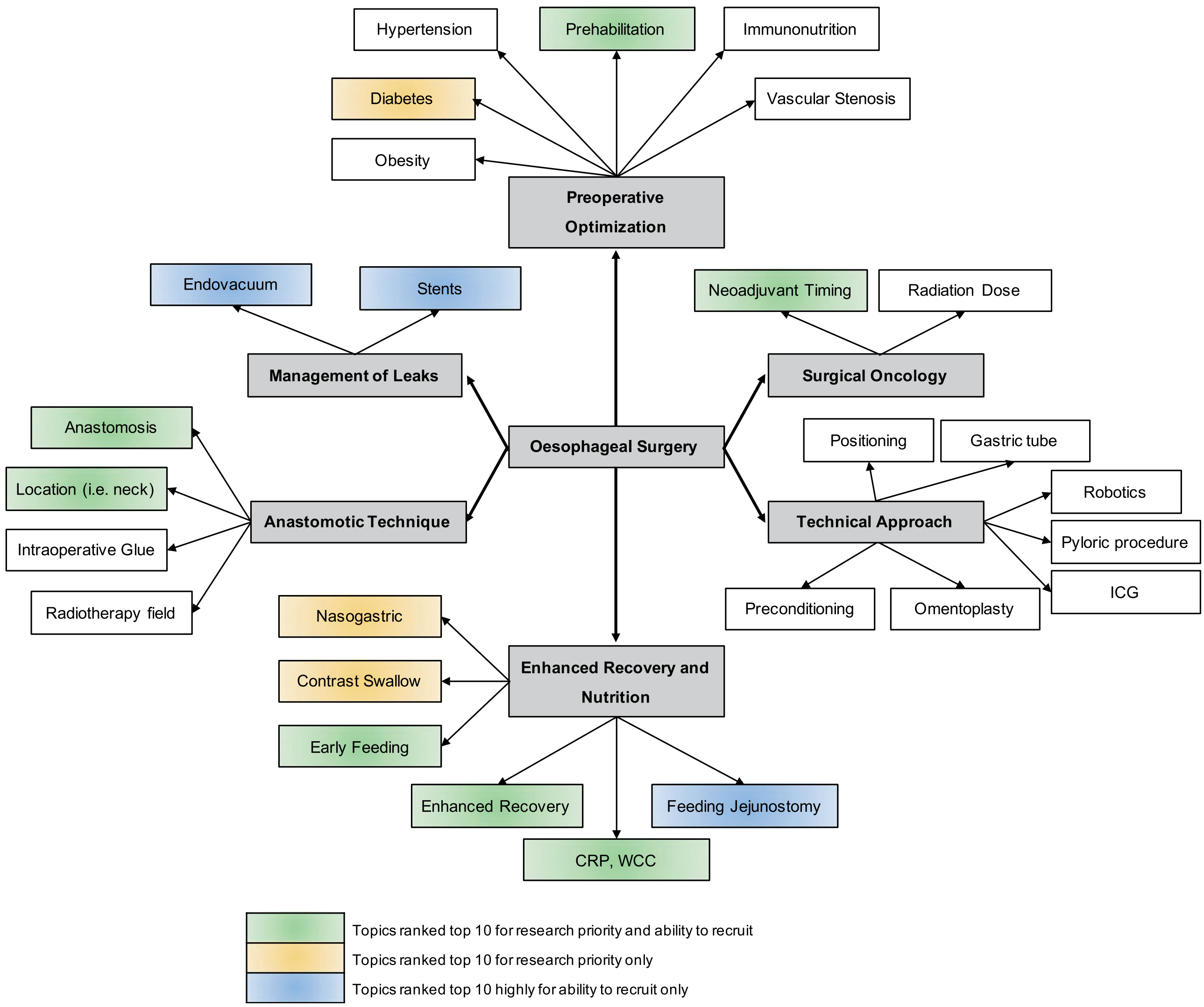

Fig. 2 Network map of topics within main research themes
ICG, indocyanine green; CRP, C-reactive protein; WCC, white cell count.

were analysed using the Mann–Whitney *U* test for comparisons across two groups, and the Kruskal–Wallis test for comparisons of more than two groups. Stratified analyses were performed for responses from the second voting round by: country income, stratified into high-income countries (HICs) and low/middle-income countries (LMICs), according to the United Nations Human Development Index; seniority of the respondent (consultant, trainee); self-declared level of operative experience (assisting, supervised, independent); and surgeon volume (50 or fewer, 51–100, over 100 procedures; only applies to consultant surgeons). $P < 0.050$ was considered statistically significant. Data analysis was performed using R version 3.2.2, with TableOne, ggplot2, Hmisc, Matchit, and survival packages (R Foundation for Statistical Computing, Vienna, Austria).

Results

Stage 1: Evidence-base mapping

The RCTs identified by evidence-base mapping were generally single-centre studies, with generalizability largely limited by the lack of international multicentre uptake[30]. Based on the subjects of these studies, and initial discussions with the steering committee, a total of 27 different research topics were developed. These topics were categorized into six broad domains: preoperative optimization, surgical oncology, technical approach, anastomotic technique, enhanced recovery and nutrition, and management of leaks (*Fig. 2*). These thematic domains each incorporated several research topics, which were agreed on by the steering committee before proceeding to the next stage (*Table 1*).

Stage 2: first voting round

During the first voting round, a total of 192 unique and complete responses were received by participants from 34 countries (154 HICs, 38 LMICs). In this round, 154 of 192 respondents (80.2 per cent) were from HICs, 159 (82.8 per cent) were consultants, and 136 (70.8 per cent) operated independently. Of the 192 respondents, 17 (8.9 per cent) were from the East. Of the consultant surgeons, 89 of 157 (56.7 per cent) were high-volume surgeons (over 100 operations) (*Table S2*). Results from the first round of voting are summarized in *Table S3*. Overall Cronbach's α was 0.90 and 0.89 for research priority and ability to recruit respectively, suggesting good internal reliability.

Table 1 Summary of research topics from voting in stage 3 on research priority for RCTs stratified by country income

	Score*			P†
	Overall	LMICs	HICs	
Preoperative optimization				
Does preoperative optimization of hypertension affect anastomotic leak rate?	2.6(1.0)	3.0(1.3)	2.5(0.9)	0.111
Does preoperative optimization of diabetes affect anastomotic leak rate?	3.6(0.9)	3.9(0.8)	3.6(0.9)	0.201
Does preoperative optimization of obesity affect anastomotic leak rate?	3.5(1.0)	3.6(0.9)	3.4(1.0)	0.606
Does prehabilitation, such as with improvement in lung function or exercise capacity, affect anastomotic leak rate?	4.1(0.8)	4.0(0.9)	4.2(0.8)	0.660
Does the aggressive management of abdominal vascular stenosis (i.e., coeliac axis stenosis) via angiography and stenting affect anastomotic leak rate?	2.9(1.0)	3.2(1.0)	2.9(1.0)	0.288
Does immunonutrition affect anastomotic leak rate?	3.1(1.1)	3.0(1.0)	3.1(1.1)	0.420
Surgical oncology				
Does the time from completion of chemoradiotherapy/radiotherapy affect anastomotic leak rate?	4.0(0.8)	3.8(0.8)	4.1(0.8)	0.147
Technical approach				
Does patient positioning during MIO affect anastomotic leak rate?	2.4(1.0)	2.5(1.2)	2.4(1.0)	0.821
Does the use of a minimally invasive approach to oesophagectomy affect anastomotic leak rate?	3.7(0.9)	3.7(1.0)	3.7(0.9)	0.791
Do robotic-assisted techniques for oesophagectomy affect anastomotic leak rate?	3.1(1.1)	3.3(1.1)	3.1(1.2)	0.484
Does the width of the gastric tube (thin tube, standard tube *versus* whole stomach) in an oesophagectomy affect anastomotic leak rate?	3.7(0.8)	3.6(0.9)	3.8(0.8)	0.318
Does the addition of a pyloric procedure (pyloroplasty, dilatation or botulinum toxin) affect anastomotic leak rate?	3.3(1.1)	3.6(0.9)	3.2(1.1)	0.153
Does ischaemic preconditioning of the stomach affect anastomotic leak rate?	3.2(1.1)	3.3(1.3)	3.2(1.1)	0.942
Does the addition of an omentoplasty affect anastomotic leak rate?	3.4(1.1)	3.4(1.1)	3.4(1.1)	0.883
Does intraoperative assessment of gastric conduit perfusion with indocyanine green assessment or intraoperative fluorescence imaging affect anastomotic leak rate?	3.7(1.0)	4.0(1.0)	3.6(1.0)	0.088
Anastomotic technique				
Does the anastomotic technique (handsewn *versus* linear stapled *versus* circular stapled) affect anastomotic leak rate?	4.1(0.9)	4.3(0.8)	4.1(0.9)	0.409
Does the location of the anastomosis (thoracic *versus* cervical) affect anastomotic leak rate?	4.0(1.0)	3.9(1.1)	4.0(1.0)	0.490
Does the addition of intraoperative glue over the anastomosis affect anastomotic leak rate?	2.6(1.1)	2.8(1.2)	2.6(1.1)	0.734
Does placing the anastomosis outside the radiotherapy field affect anastomotic leak rate?	3.7(0.9)	3.7(1.0)	3.7(0.9)	0.925
Enhanced recovery and nutrition				
Does the duration of postoperative nasogastric decompression affect anastomotic leak rate?	3.5(1.1)	3.7(1.0)	3.5(1.1)	0.464
Does the routine use of postoperative contrast swallow or other forms of anastomotic integrity assessment facilitate early intervention and affect outcomes of anastomotic leak after oesophagectomy?	3.4(1.2)	3.5(1.1)	3.4(1.2)	0.858
Does early postoperative oral feeding affect anastomotic leak rate?	3.8(0.9)	3.9(0.9)	3.8(1.0)	0.551
Does the use of enhanced recovery protocols affect anastomotic leak rate?	3.9(0.9)	3.9(1.1)	3.9(0.9)	0.656
Does the regular monitoring of CRP, WCC or a combination of laboratory markers in the postoperative period facilitate early detection of anastomotic leak after oesophagectomy?	3.9(1.0)	4.0(1.1)	3.9(0.9)	0.399
Does routine placement of a feeding jejunostomy *versus* expectant management, with intervention (NJ, feeding jejunostomy, TPN) only if leak identified, have an impact on outcomes following anastomotic leak?	3.8(1.1)	4.1(0.8)	3.8(1.1)	0.181
Management of leaks				
Is there a significant role for endoscopic stenting in management of anastomotic leak?	3.8(1.1)	4.1(0.8)	3.7(1.1)	0.172
Does endovacuum therapy have a significant role in management of anastomotic leak?	3.9(0.9)	4.0(0.9)	3.9(0.9)	0.672

*Values are mean(s.d.) score on a five-point Likert scale representing the research priority for a RCT on the stated topic; higher scores represent a higher research priority. MIO, minimally invasive oesophagectomy; CRP, C-reactive protein; WCC, white cell count; NJ, naso-jejunal; TPN, total parenteral nutrition. †Low/middle-income countries (LMICs) *versus* high-income countries (HICs) (Mann–Whitney U test).

Table 2 Summary of research topics from voting in stage 3 on ability to recruit for RCTs stratified by country income

	Score*			P†
	Overall	LMICs	HICs	
Preoperative optimization				
Does preoperative optimization of hypertension affect anastomotic leak rate?	3.2(1.0)	3.3(1.2)	3.2(1.1)	0.3
Does preoperative optimization of diabetes affect anastomotic leak rate?	3.7(0.9)	3.7(1.0)	3.6(0.9)	0.2
Does preoperative optimization of obesity affect anastomotic leak rate?	3.3(1.1)	3.2(1.2)	3.3(1.1)	0.9
Does prehabilitation, such as with improvement in lung function or exercise capacity, affect anastomotic leak rate?	3.9(0.9)	3.9(1.1)	3.8(0.9)	0.5
Does the aggressive management of abdominal vascular stenosis (i.e., coeliac axis stenosis) via angiography and stenting affect anastomotic leak rate?	2.4(1.1)	2.4(1.3)	2.4(1.1)	1.0
Does immunonutrition affect anastomotic leak rate?	3.1(1.2)	3.1(1.5)	3.2(1.1)	0.9
Surgical oncology				
Does the time from completion of chemoradiotherapy/radiotherapy affect anastomotic leak rate?	3.8(1.0)	3.8(1.1)	3.9(1.0)	0.7
Technical approach				
Does patient positioning during MIO affect anastomotic leak rate?	2.6(1.2)	2.7(1.4)	2.7(1.2)	0.7
Does the use of a minimally invasive approach to oesophagectomy affect anastomotic leak rate?	3.3(1.2)	2.9(1.3)	3.4(1.2)	0.002
Do robotic-assisted techniques for oesophagectomy affect anastomotic leak rate?	2.4(1.3)	1.9(1.1)	2.6(1.4)	< 0.001
Does the width of the gastric tube (thin tube, standard tube *versus* whole stomach) in an oesophagectomy affect anastomotic leak rate?	3.5(1.0)	3.8(1.0)	3.5(1.1)	0.046
Does the addition of a pyloric procedure (pyloroplasty, dilatation or botulinum toxin) affect anastomotic leak rate?	3.4(1.2)	3.3(1.3)	3.4(1.2)	0.9
Does ischaemic preconditioning of the stomach affect anastomotic leak rate?	2.7(1.2)	3.2(1.4)	2.6(1.2)	< 0.001
Does the addition of an omentoplasty affect anastomotic leak rate?	3.4(1.2)	3.2(1.3)	3.4(1.1)	0.2
Does intraoperative assessment of gastric conduit perfusion with indocyanine green assessment or intraoperative fluorescence imaging affect anastomotic leak rate?	3.2(1.2)	2.6(1.3)	3.3(1.2)	< 0.001
Anastomotic technique				
Does the anastomotic technique (handsewn *versus* linear stapled *versus* circular stapled) affect anastomotic leak rate?	3.9(1.1)	3.8(1.2)	3.8(1.1)	0.9
Does the location of the anastomosis (thoracic *versus* cervical) affect anastomotic leak rate?	3.6(1.1)	3.8(1.2)	3.4(1.2)	0.012
Does the addition of intraoperative glue over the anastomosis affect anastomotic leak rate?	2.8(1.3)	2.6(1.3)	2.9(1.3)	0.1
Does placing the anastomosis outside the radiotherapy field affect anastomotic leak rate?	3.2(1.1)	2.9(1.2)	3.2(1.1)	0.1
Enhanced recovery and nutrition				
Does the duration of postoperative nasogastric decompression affect anastomotic leak rate?	3.6(1.0)	3.4(1.2)	3.6(1.1)	0.3
Does the routine use of postoperative contrast swallow or other forms of anastomotic integrity assessment facilitate early intervention and affect outcomes of anastomotic leak after oesophagectomy?	3.6(1.1)	3.6(1.2)	3.6(1.2)	0.9
Does early postoperative oral feeding affect anastomotic leak rate?	3.7(1.0)	3.7(1.1)	3.7(1.0)	0.8
Does the use of enhanced recovery protocols affect anastomotic leak rate?	3.8(1.0)	3.8(1.1)	3.7(1.1)	0.3
Does the regular monitoring of CRP, WCC or a combination of laboratory markers in the postoperative period facilitate early detection of anastomotic leak after oesophagectomy?	3.9(1.0)	3.7(1.2)	4.0(1.0)	0.024
Does routine placement of a feeding jejunostomy *versus* expectant management, with intervention (NJ, feeding jejunostomy, TPN) only if leak identified, have an impact on outcomes following anastomotic leak?	3.5(1.1)	3.6(1.2)	3.5(1.1)	0.4
Management of leaks				
Is there a significant role for endoscopic stenting in management of anastomotic leak?	3.4(1.1)	3.2(1.4)	3.4(1.2)	0.3
Does endovacuum therapy have a significant role in management of anastomotic leak?	3.3(1.2)	2.6(1.3)	3.5(1.2)	< 0.001

*Values are mean(s.d.) score on a five-point Likert scale representing ability to recruit for an RCT on the stated topic; higher scores represent a greater ability to recruit. MIO, minimally invasive oesophagectomy; CRP, C-reactive protein; WCC, white cell count; NJ, naso-jejunal; TPN, total parenteral nutrition. †Low/middle-income countries (LMICs) *versus* high-income countries (HICs) (Mann–Whitney *U* test).

Table 3 Summary of top ten research priorities for RCTs from voting in stage 3

	Score*		
	Overall	LMICs	HICs
Does prehabilitation, such as with improvement in lung function or exercise capacity, affect anastomotic leak rate?	4.1†	4.0‡	4.2§
Does the anastomotic technique (handsewn *versus* linear stapled *versus* circular stapled) affect anastomotic leak rate?	4.1†	4.3‡	4.1§
Does the time from completion of chemotherapy/radiotherapy affect anastomotic leak rate?	4.0†	3.8	4.1§
Does the location of the anastomosis (thoracic *versus* cervical) affect anastomotic leak rate?	4.0†	3.9	4.0§
Does the use of enhanced recovery protocols affect anastomotic leak rate?	3.9†	3.9‡	3.9§
Does the regular monitoring of CRP, WCC or a combination of laboratory markers in the postoperative period facilitate early detection of anastomotic leak after oesophagectomy?	3.9†	4.0‡	3.9§
Does endovacuum therapy have a significant role in management of anastomotic leak?	3.9	4.0	3.9
Does early postoperative oral feeding affect anastomotic leak rate?	3.8†	3.9‡	3.8§
Does routine placement of a feeding jejunostomy *versus* expectant management, with intervention (NJ, feeding jejunostomy, TPN) only if leak identified, have an impact on outcomes following of anastomotic leak?	3.8	4.1‡	3.8
Is there a significant role for endoscopic stenting in management of anastomotic leak?	3.8	4.1	3.7

*Values are mean scores on a five-point Likert scale; higher scores represent a higher research priority, or a greater ability to recruit. The ten topics with the highest research priority are reported, and are sorted in descending order of mean Likert score. †Top 10 topics on ability to recruit in overall respondents; ‡top 10 topics on ability to recruit in low/middle-income country (LMIC) respondents; §top 10 topics on ability to recruit in high-income country (HIC) respondents.

Stage 3: second voting round

During the second round, a total of 171 unique and complete responses were received by participants from 34 countries (137 HICs, 34 LMICs) (Supplementary Figure 1). In this round, 137 of 171 respondents (80.1 per cent) were from HICs, 148 (86.5 per cent) were consultants, 126 (73.7 per cent) performed surgery independently, and 86 of 146 consultants (58.9 per cent) were high-volume surgeons (over 100 operations). Of the 171 respondents, 14 (8.2 per cent) were from the East. Comparisons between stages 2 and 3 showed no significant differences in respondent characteristics (*Table S2*), and the responses relating to research priorities and ability to recruit also remained consistent between the two stages. Overall Cronbach's α was 0.93 and 0.91 for research priority and ability to recruit respectively, suggesting good internal reliability.

Research priority

High-scoring research topics based on research priority included prehabilitation, anastomotic techniques, timing of surgery after neoadjuvant chemoradiotherapy, and location of anastomosis (*Table 1*). Analysis stratified by country income (*Table 1*) and respondent grade (trainee *versus* consultant) (*Table S4*) did not demonstrate any significant difference in mean research priority scores for any of the topics considered. Stratified analyses by level of operative experience and surgeon volume demonstrated minimal differences in research priorities (*Tables* S5 and S6 respectively).

Ability to recruit

High-scoring research topics based on ability to recruit included prehabilitation, anastomotic techniques, regular postoperative biochemical monitoring, and timing of surgery after neoadjuvant chemoradiotherapy (*Table 2*). Analysis stratified by country income demonstrated significantly lower priority by LMIC respondents for recruitment to RCTs involving a technical approach (such as minimally invasive, width of gastric tube, ischaemic preconditioning) and location of anastomosis.

Top ten research topics

Highly ranked topics by research priority and ability to recruit were prehabilitation, anastomotic techniques, timing of surgery after neoadjuvant chemoradiotherapy, regular postoperative biochemical monitoring, and location of anastomosis. The top ten research topics and concordance with ability to recruit are summarized in *Table 3* and *Fig. 2*.

Discussion

The main strength of this Delphi study is the broad inclusion of specialist surgeons in LMICs and HICs. However, there are limitations, including that there was no patient or public involvement, and there were non-responders at the third stage, an inherent issue with Delphi methodology[23]. Although 30 per cent of respondents were senior trainees or non-independent surgeons, subset analysis of only consultants/attending surgeons did not alter the findings.

There is a lack of high-quality RCTs in surgery assessing techniques to reduce anastomotic leaks after oesophagectomy[21,31]. As a result, current clinical practice is generally driven by local centre and anecdotal experience. For instance, the choice of anastomotic technique varies between units and among individual surgeons within a unit[10]. This is likely to reflect a deficiency in current evidence in this area, with RCTs being limited to those with small sample sizes, with variation in individual techniques and surgical approach, and patients with mixed indications being included. The Delphi process identified assessment of outcomes by anastomotic technique to be one of the top three topics for research priority. Because of similar issues, the benefits of pyloric procedures and omentoplasty remain an ongoing debate[30,32].

There is growing evidence for the benefits of prehabilitation in major abdominal surgery, with early studies demonstrating lower rates of postoperative pulmonary and cardiac complications[33–35]. Ongoing trials[36–39] may help improve the current evidence base. However, owing to the variation in prehabilitation regimens published, traditional two-arm or three-arm RCTs may not represent the best methodology[40]. For instance, current regimens include a combination of physical fitness (supervised or non-supervised), psychological interventions or nutritional aspects, such that data may not be generalizable between published RCTs. Furthermore, current RCTs may be underpowered due to small sample sizes, precluding reliable interpretation of study findings. Instead, adaptive RCT designs with large sample sizes may be the optimal approach to improving the evidence base[41].

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Supplementary material

Supplementary material is available at *BJS* online.

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